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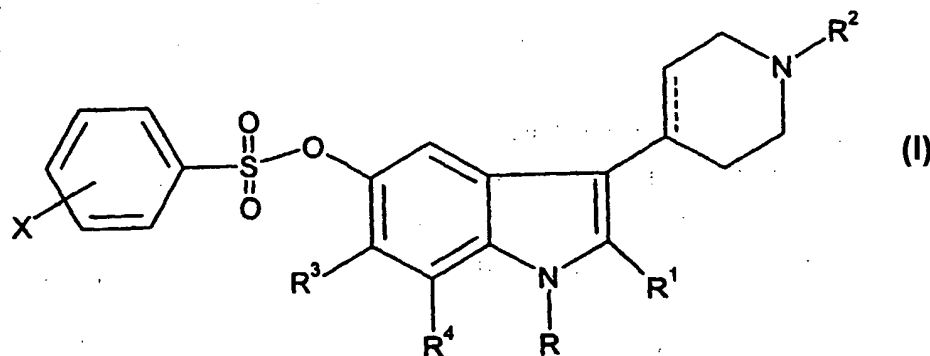
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(54) Title: BENZENESULFONIC ACID INDOL-5-YL ESTERS AS ANTAGONISTS OF THE 5-HT₆ RECEPTOR



(57) Abstract: The present invention relates to compounds of formula I: which are antagonists of 5-HT₆ receptor.



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**BENZENESULFONIC ACID INDOL-5-YL ESTERS
AS ANTAGONISTS OF THE 5-HT₆ RECEPTOR**

The present invention relates to the field of
5 pharmaceutical and organic chemistry and is concerned with
compounds which are antagonists of the 5-HT₆ receptor.

The 5-HT₆ receptor is a member of the G-protein coupled
receptor superfamily of serotonin receptors, and, like the
10 5-HT₄ and 5-HT₇ receptors, it is positively coupled to
adenylate cyclase.¹ The rat 5-HT₆ receptor was first cloned
in 1993^{2,3} and the cloning of the human homologue, to which
it shares a 89% sequence identity, was reported in 1996.⁴
The localization of 5-HT₆ receptors in rat brain has been
15 studied using mRNA quantification by Northern analysis and
RT-PCR, immunohistochemistry, and autoradiography.^{2, 3, 5, 6, 7,}
⁸ These methods have consistently found high levels of the
receptor in olfactory tubercle, hippocampus, striatum,
nucleus accumbens, and cortical regions. 5-HT₆ receptors are
20 either absent or present in very low levels in peripheral
tissues.^{2, 3}

To date, there are no known high affinity, selective
agonists at the 5-HT₆ receptor. Serotonin itself has only
moderate affinity for the 5-HT₆ receptor (K_i = 65 nM) and
25 the most selective agonist reported to date, N,N-dimethyl-2-
ethyl-5-methoxytryptamine, has K_i = 81 nM and only 3.5-fold
selectivity versus the 5-HT_{2A} receptor.⁹

Much of the recent interest in the 5-HT₆ receptor is
30 due to the observation that several psychotropic agents are
high affinity antagonists at the human 5-HT₆ receptor.^{4, 10}
These compounds include amitriptyline (K_i = 65 nM) and the
atypical antipsychotics clozapine (K_i = 9.5 nM), olanzapine
(K_i = 10 nM), and quetiapine (33 nM). None of these
35 compounds, however, are selective. The first selective 5-HT₆
receptor antagonists reported are Ro 04-6790 and Ro 63-0563.

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Their usefulness is limited by their moderate affinity (K_i = 50nM and 12 nM, respectively) and poor pharmacokinetics.¹¹ A series of 5-HT₆ receptor antagonists, culminating in SB-271,046, has been reported.¹² This compound has high
5 affinity (K_i = 1.2 nM) and selectivity (>200-fold versus >55 receptors, enzymes and ion channels) and is 80% bioavailable. A selective radioligand [¹²⁵I]-SB-258,585 has been used for radioligand binding and autoradiographic studies.^{13, 14} These compounds are useful tools for
10 preclinical studies on the 5-HT₆ receptor. No clinical studies with any selective 5-HT₆ receptor antagonists have been reported.

The rationale for the use of selective 5-HT₆ receptor antagonists to treat cognitive dysfunction is based on three
15 lines of reasoning: the ability of selective 5-HT₆ receptor antagonists to modulate cholinergic and glutamatergic neuronal function, clinical studies of the atypical antipsychotics clozapine and olanzapine on cognitive function, the activity of selective 5-HT₆ receptor
20 antagonists in animal models of cognitive function.

Selective 5-HT₆ receptor antagonists modulate cholinergic and glutamatergic neuronal function. Cholinergic and glutamatergic neuronal systems play important roles in cognitive function. Cholinergic neuronal pathways are known
25 to be important to memory formation and consolidation. Centrally acting anticholinergic agents impair cognitive function in animal and clinical studies and loss of cholinergic neurons is one of the hallmarks of Alzheimer's disease. Conversely, stimulation of cholinergic function has
30 been known to improve cognitive performance and the only two agents currently approved for the treatment of cognitive deficit in Alzheimer's disease, tacrine and donepezil, are both acetylcholinesterase inhibitors. The glutamatergic system in the prefrontal cortex is also known to be involved
35 in cognitive function.^{26, 27}

Blocking 5-HT₆ receptor function has been shown to elicit procholinergic effects *in vivo*. Administration (icv)

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to rats of antisense oligonucleotides targeting the 5-HT₆ receptor sequence induced yawning and stretching behavior that was blocked by the cholinergic antagonist atropine.¹⁵ The selective 5-HT₆ receptor antagonist Ro 04-6790 induced stretching behavior in a dose-dependent manner. This behavior was blocked by the centrally acting anticholinergic agents scopolamine and atropine but not by methyl-scopolamine at doses known to be peripherally selective.¹⁶ Ro 04-6790 was also shown to block the rotation behavior induced by scopolamine administration to rats with unilateral nigrostriatal 6-OH-DA lesions. It did not block rotational behavior induced by L-DOPA or amphetamine.¹⁷ Ro 04-6790 reversed scopolamine induced performance deficits in the object recognition test, a model of cognitive function. Another selective 5-HT₆ receptor antagonist, SB-271046, potentiated the yawning behavior induced by the cholinesterase inhibitor physostigmine.¹⁸ These studies suggest that 5-HT₆ receptor blockade facilitates cholinergic transmission. In vivo microdialysis studies, SB-271,046 (10 mg/kg, sc) increases glutamate release in the prefrontal cortex through a neuronal mechanism.²⁵

Clinical studies of the atypical antipsychotics clozapine and olanzapine on cognitive function. The atypical antipsychotics clozapine and olanzapine are both high affinity, albeit nonselective, 5-HT₆ receptor antagonists.⁴ On the other hand, risperidone and the typical antipsychotic haloperidol do not have significant affinity for the 5-HT₆ receptor. Clinical differences seen with these sets of drugs may be attributable to 5-HT₆ receptor blockade. Goldberg et al. reported no beneficial cognitive effect of clozapine treatment in a small (N = 15) trial in treatment resistant schizophrenics.¹⁹ In contrast, Meltzer et al.²⁰ in a larger study of treatment-resistant schizophrenics (N = 36), observed improvements in several domains of neuropsychological function at six weeks and six months following initiation of clozapine treatment. In non-treatment resistant schizophrenics, clozapine was more

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effective than placebo in improving cognitive function by several measures.²¹ This effect was seen at six months and persisted throughout the 12 month study. The effect of olanzapine, risperidone, and haloperidol on cognitive function has been compared in a multicenter, double blind study in schizophrenics.²² The olanzapine group showed a statistically significant improvement in cognitive function over either haloperidol or risperidone treatment. This effect was apparent after 6 weeks treatment and continued throughout the 54 weeks of the study. Animal studies suggest that these effects could be mediated through the release of acetylcholine in the prefrontal cortex.²³

Activity of selective 5-HT₆ receptor antagonists in animal models of cognitive function. With the recent development of the selective 5-HT₆ receptor antagonists Ro-04,6790 and SB-271,046, there have been several reports on the activity of these compounds in models of cognitive function. The selective 5-HT₆ receptor antagonist SB-271,046 improved performance in the Morris water maze.²⁴ These results are consistent with the finding that chronic icv administration of antisense oligonucleotides directed toward the 5-HT₆ receptor sequence led to improvements in some measures of performance in the Morris water maze.¹⁶ SB-271,046 treatment also led to improvements in the spatial alternation operant behavior test in aged rats.²⁴

The compounds of the present invention are selective, high affinity antagonists of 5-HT₆, and thus, provide a valuable treatment for 5-HT₆ receptor mediated disorders.

Background References

1. Branchek, T. A., et al. (2000). *Annu Rev Pharmacol Toxicol* 40: 319-34.
2. Monsma, F. J., Jr., et al. (1993). *Mol Pharmacol* 43(3): 320-7.
3. Ruat, M., et al. (1993). *Biochem Biophys Res Commun* 193(1): 268-76.
4. Kohen, R., et al. (1996). *J Neurochem* 66(1): 47-56.

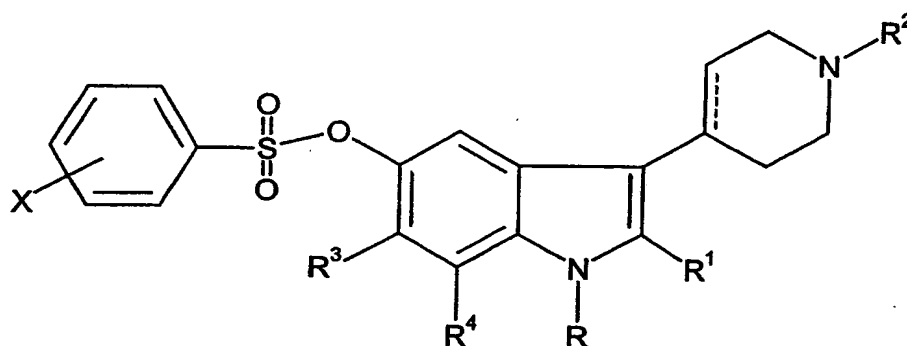
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5. Ward, R. P., et al. (1996). J Comp Neurol 370(3): 405-14.
6. Ward, R. P., et al. (1995). Neuroscience 64(4): 1105-11.
7. Gerard, C., et al. (1997). Brain Res 746(1-2): 207-19.
- 5 8. Gerard, C., et al. (1996). Synapse 23(3): 164-73.
9. Glennon, R. A., et al. (2000). J Med Chem 43(5): 1011-8.
10. Roth, B. L., et al. (1994). J Pharmacol Exp Ther 268(3): 1403-10.
11. Sleight, A. J., et al. (1998). Br J Pharmacol 124(3): 556-62.
- 10 12. Routledge, C., et al. (2000). Br. J. Pharmacol. 130(7): 1606.
13. Hirst, W. D., et al. (1999). Br. J. Pharmacol. Suppl. ((in press)).
- 15 14. Hirst, W. D., et al. (2000). Br. J. Pharmacol. 130: 1597.
15. Bourson, A., et al. (1995). J Pharmacol Exp Ther 274(1): 173-80.
16. Bentley, J. C., et al. (1999). Br J Pharmacol 126(7): 1537-42.
- 20 17. Bourson, A., et al. (1998). Br J Pharmacol 125(7): 1562-6.
18. Routledge, C., et al. (1999). Br. J. Pharmacol. 127(Suppl.): 21P.
- 25 19. Goldberg, T. E., et al. (1993). Br J Psychiatry 162: 43-8.
20. Hagger, C., et al. (1993). Biol Psychiatry 34(10): 702-12.
21. Lee, M. A., et al. (1994). J Clin Psychiatry 55 Suppl B: 82-7.
- 30 22. Purdon, S. E., et al. (2000). Arch Gen Psychiatry 57(3): 249-58.
23. Parada, M. A., et al. (1997). J Pharmacol Exp Ther 281(1): 582-8.
- 35 24. Rogers, D. C., et al. (1999). Br J Pharamcol 127(suppl.): 22P.

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25. Dawson, L. A., et al. (2000). Br J Pharmacol 130(1): 23-6.
26. Dudkin, K. N., et al. (1996). Neurosci Behav Physiol 26(6): 545-51.
- 5 27. Koechlin, E., et al. (1999). Nature 399(6732): 148-51.

The present invention provides compounds of formula I:



formula I

10 wherein

R is hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkylsulfonyl, phenylsulfonyl, substituted phenylsulfonyl, naphthylsulfonyl, benzylsulfonyl, or substituted benzylsulfonyl;

15

R¹ is hydrogen or C₁-C₃ alkyl or where R⁴ is hydrogen, C₁-C₆ alkyl, or halo then R¹ and R may be taken together to form -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂-;

20 R² is hydrogen or C₁-C₆ alkyl;

R³ is hydrogen or halo;

25 R⁴ is hydrogen, C₁-C₆ alkyl, vinyl, allyl, C₂-C₆ alkynyl, or halo or when R¹ is hydrogen or C₁-C₃ alkyl then R⁴ and R may be taken together to form -CH₂-CH₂-CH₂-;

X is 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, C₁-C₆ alkyl, C₁-C₆

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alkoxy, nitro, amino, C₁-C₆ alkylsulfonylamino, and cyano or X is 5 halo substituents;

|||
represents either a single or a double bond;
and pharmaceutically acceptable addition salts thereof.

5 The present invention also provides for novel pharmaceutical compositions, comprising: a compound of the formula I and a pharmaceutically acceptable diluent.

Because the compounds of formula I are antagonists of 5-HT₆ receptor, the compounds of formula I are useful for
10 the treatment of a variety of disorders, including:
cognitive disorders, age-related cognitive disorder, mild cognitive impairment, mood disorders (including depression, mania, bipolar disorders), psychosis (in particular schizophrenia), anxiety (particularly including generalized
15 anxiety disorder, panic disorder, and obsessive compulsive disorder), idiopathic and drug-induced Parkinson's disease, epilepsy, convulsions, migraine (including migraine headache), substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol,
20 benzodiazepines, cocaine, sedatives, hypnotics, etc.), sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, conduct disorder, learning disorders, dementia (including Alzheimer's disease and AIDS-induced dementia), Huntington's Chorea, cognitive deficits
25 subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage, vascular dementia, multi-infarct dementia, amyotrophic lateral sclerosis, and multiple sclerosis,
30 comprising: administering to a patient in need thereof an effective amount of a compound of formula I.

In another embodiment the present invention provides methods of treating disorders associated with the 5-HT₆ receptor, comprising: administering to a patient in need
35 thereof an effective amount of a compound of formula I.

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That is, the present invention provides for the use of a compound of formula I or pharmaceutical composition thereof for the treatment disorders associated with the 5-HT₆ receptor.

5

Detailed Description of the Invention

As used herein, the following terms have the meanings indicated:

10 The term "C₁-C₃ alkyl straight or branched alkyl chain having from one to three carbon atoms, and includes methyl, ethyl, propyl, and iso-propyl.

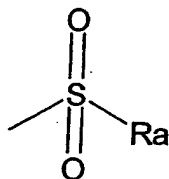
15 The term "C₁-C₆ alkyl" refers to a straight or branched alkyl chain having from one to six carbon atoms, and includes methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, pentyl, hexyl, and the like.

20 The term "substituted C₁-C₆ alkyl" refers to a straight or branched alkyl chain having from one to six carbon atoms and having 1 or 2 substituents selected from the group consisting of C₃-C₆ cycloalkyl, phenyl, substituted phenyl, pyridyl, and trifluoromethyl.

25 The term "C₁-C₆ alkoxy" refers to a straight or branched alkyl chain having from one to six carbon atoms attached through an oxygen atom, and includes methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *sec*-butoxy, *t*-butoxy, pentoxy, hexoxy, and the like.

30 The term "C₃-C₆ cycloalkyl" refers to refers to saturated cyclic alkyl group having from three to six carbon atoms and includes, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

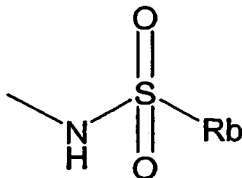
The term "C₁-C₆ alkylsulfonyl" refers to a radical of the formula



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wherein R_a is a C_1-C_6 alkyl.

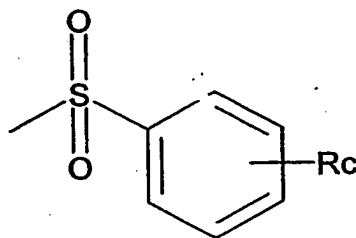
The term " C_1-C_6 alkylsulfonylamino" refers to a radical of the formula



5 wherein R_b is a C_1-C_6 alkyl.

The term " C_3-C_6 cycloalkyl" refers to a saturated cyclic alkyl group having from three to six carbon atoms and includes, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

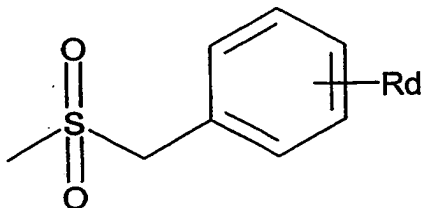
10 The term "substituted phenylsulfonyl" refers to a radical of the formula



15 wherein R_c is from 1 to 3 groups independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, cyano, trifluoromethyl, nitro, and phenyl.

The term "substituted benzylsulfonyl" refers to a radical of the formula

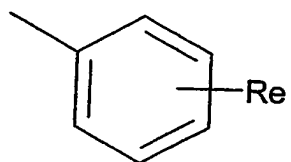
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25 wherein R_d is from 1 to 3 groups independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, cyano, trifluoromethyl, and nitro.

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The term "substituted phenyl" refers to a radical of the formula



5 wherein R_e is from 1 to 3 groups independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, cyano, trifluoromethyl, nitro, and phenyl.

10 The term " C_2 - C_6 alkynyl" refers to a radical of the formula



wherein R_f is selected from the group consisting of hydrogen and C_1 - C_4 alkyl.

15 The term " C_1 - C_4 alkyl" refers to a straight or branched alkyl chain having from one to four carbon atoms, and includes methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

The terms "halogen" and "halo" refer to a chloro, fluoro, bromo or iodo atom.

20 The term "pharmaceutically-acceptable addition salt" refers to an acid addition salt.

The compound of formula I and the intermediates described herein form pharmaceutically acceptable acid addition salts with a wide variety of organic and inorganic acids and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. A pharmaceutically-acceptable addition salt is formed from a pharmaceutically-acceptable acid as is well known in the art. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2-19 (1977) which are known to

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the skilled artisan. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydriodic, nitric, sulfuric, phosphoric, hypophosphoric, metaphosphoric, pyrophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include chloride, bromide, iodide, nitrate, acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, isobutyrate, phenylbutyrate, α -hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, caprate, caprylate, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, oxalate, phthalate, teraphthalate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, benzenesulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethylsulfonate, 2-hydroxyethylsulfonate, methylsulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, naphthalene-1,5-sulfonate, p-toluenesulfonate, xylenesulfonate, tartrate, and the like.

As with any group of pharmaceutically active compounds, some groups are preferred in their end use application. Preferred embodiments of the present invention are given

below:

Compounds in which R is hydrogen or C_1 - C_6 alkyl, R and R^1 are taken together to form $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, or R and R^4 are taken together to form $-CH_2-CH_2-CH_2-$ are preferred.

Compounds in which R is hydrogen are more preferred.

When R is C_1 - C_6 alkyl, compounds in which R is methyl are more preferred.

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Compounds in which R^1 is hydrogen or C_1-C_3 alkyl are preferred.

Compounds in which R^2 is C_1-C_6 alkyl are preferred.

Compounds in which R^2 is methyl are more preferred.

5 When R^3 is halo, the compounds in which R^3 is fluoro are preferred.

Compounds in which R^4 is hydrogen, C_1-C_6 alkyl, or halo are preferred.

Compounds in which X is halo are preferred.

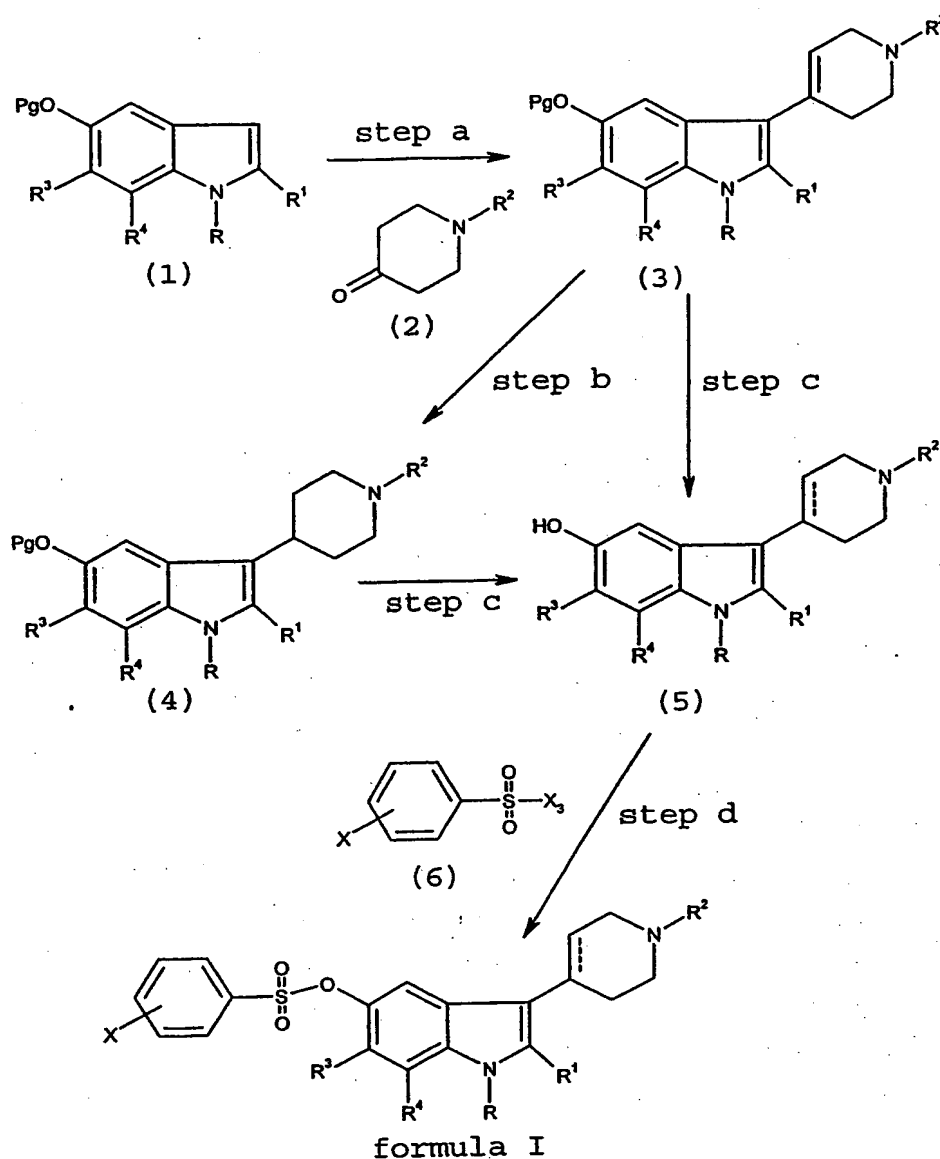
10 When X is halo, the compounds in which X is fluoro are preferred.

When X is fluoro, the compounds in which X is 2,6-difluoro are more preferred.

15 The compounds of formula I are prepared as described in Scheme A. In Scheme A all substituents, unless otherwise indicated, are as previously defined, and all reagents are well known and appreciated in the art.

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Scheme A



The specific sequence of reactions depicted in Scheme A is not critical. For many of the compounds of formula I the order of these steps can be varied to provide compounds of formula I. In addition, variation with regard to the introduction the group R, the use of protecting groups, and modification to give various R₂ and R₄ groups can be used. Some of the possible variations are discussed below.

In Scheme A, step a, an appropriate indole of formula (1) is condensed with an appropriate piperidin-4-one of formula (2) to give a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-

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indole of formula (3). An appropriate indole of formula (1) may be one in which Pg is an protecting group and R, R¹, R³, and R⁴ are as desired in the final product of formula I. The selection and use of suitable protecting groups are well known and appreciated in the art (Protecting Groups in Organic Synthesis, Theodora Greene (Wiley-Interscience)). Preferred protecting groups include methyl, benzyl, and dimethyl-t-butylsilyl. As one of the variations mentioned above, the indoles of formula (1) having a 5-hydroxy, are also suitable for the reaction in step a. Thus, an appropriate indole of formula (1) is also one having a 5-hydroxy, instead of the protected hydroxy depicted. Such unprotected compound of formula (1), when used, directly give compounds of formula (5). Also, as will be appreciated by the skilled person, the indoles of formula (1) in which R is hydrogen can give rise upon alkylation or sulfonation at a later point, to compounds of formula I in which R is not hydrogen. An appropriate piperidin-4-one of formula (2) is most conveniently one in which R² is as desired in the final product of formula I.

Appropriate indoles of formula (1) are generally available from commercial sources. Appropriate indoles of formula (1) can also be prepared by methods described herein and by methods described in the art, for example, Robinson, The Fischer Indole Synthesis, Wiley, New York (1983); Hamel, et al., Journal of Organic Chemistry, 59, 6372 (1994); and Russell, et al., Organic Preparations and Procedures International, 17, 391 (1985). Appropriate piperidin-4-ones of formula (2) are readily available and can be prepared by the alkylation of piperidin-4-one.

For example in step a, an appropriate indole of formula (1) is condensed with an appropriate piperid-4-one of formula (2) to give a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3). When the appropriate indole of formula (1) is one in which R is hydrogen, the reaction is typically carried out in the presence of a suitable base, typically sodium hydroxide, potassium hydroxide, sodium

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alkoxide, (such as sodium methanolate or sodium ethanolate), or potassium alkoxide, (such as potassium methanolate, potassium ethanolate, or potassium t-butoxide). The reaction is carried out in a suitable solvent, such as methanol, ethanol, tetrahydrofuran, or mixtures of methanol or ethanol and tetrahydrofuran. Typically, about 2 molar equivalents of piperid-4-one of formula (2) are used. The reaction is generally carried out at temperatures of about 40°C to the reflux temperature of the selected solvent. The reaction typically requires 8-72 hours. In general, the basic conditions are favored for the condensation above compounds of formula (1) in which Pg is a protecting group. The product can be isolated and purified by techniques well known in the art, such as precipitation, filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

Alternately, for example in step a, an appropriate indole of formula (1) is condensed with an appropriate piperid-4-one of formula (2) to give a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3). The reaction may be carried out in the presence of a suitable acid, typically phosphoric acid or sulfuric acid. The reaction is carried out in a suitable solvent, such as acetic acid and water. Typically, about 2-6 molar equivalents of the piperid-4-one of formula (2) are used. The reaction is generally carried out at temperatures of about 40°C to 100°C. The reaction typically requires 8-72 hours. In general, the acidic conditions are favored for the condensation above compounds of formula (1) having a 5-hydroxy. The product can be isolated and purified by techniques well known in the art, such as precipitation, filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

Reaction Scheme A, step b, depicts the reduction of a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3) to give a 3-(piperidin-4-yl)-1H-indole of formula (4).

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For example, a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3) may be hydrogenated over a catalyst, such as palladium on carbon or platinum oxide, to give a 3-(piperidin-4-yl)-1H-indole of formula (4). Such

5 hydrogenations are generally carried out in a solvent and a variety of solvents are suitable, for example methanol, ethanol, or isopropanol, tetrahydrofuran, or mixed solvents, such as tetrahydrofuran and ethyl acetate. The

10 hydrogenation may be performed at an initial hydrogen pressure of 20-180 psi (137-1241 kPa), preferably from 50-60 psi (345-413 kPa). The reaction is typically carried out at temperature of about 0°C to about 60°C, preferably at

15 temperatures of about 40°C to 60°C. The reaction typically requires 1 hour to 3 days. The product can be isolated and purified by techniques well known in the art, such as

filtration, extraction, evaporation, trituration, precipitation, chromatography, and recrystallization.

As an alternative to hydrogenation, 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3) may be

20 converted to a 3-(piperidin-4-yl)-1H-indole of formula (4) by treatment with triethylsilane/trifluoroacetic acid, if desired. The 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3) is dissolved in trifluoroacetic acid to which is added an excess, generally 1.5-10 equivalents, of

25 triethylsilane. The reaction mixture is generally carried out at ambient temperature for about 1 to about 48 hours. The product is isolated by concentrating under reduced pressure and then treated with 2N sodium or potassium hydroxide or tartaric acid and extracting. The product can

30 be purified by techniques well known in the art, such as filtration, extraction, evaporation, trituration, precipitation, chromatography, and recrystallization.

Another alternative to the above reduction conditions, 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3)

35 may be reduced by treatment with 1-4 equivalents of sodium borohydride with or without an acid such as acetic acid or trifluoroacetic acid. The reaction is generally carried out

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in a solvent, such as tetrahydrofuran. The reaction is typically carried out at temperature of from about 0°C to about 60°C, most conveniently at ambient temperature. The reaction typically requires 1 to 3 hours. The product can
5 be isolated and purified by techniques well known in the art, such as precipitation, filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

As one of the variations discussed above, this is a
10 convenient point in the synthesis to alkylate or sulfonate, if desired, a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3) or a 3-(piperidin-4-yl)-1H-indole of formula (4) in which R is hydrogen.

For example, a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-
15 indole of formula (3) or a 3-(piperidin-4-yl)-1H-indole of formula (4) is contacted with an appropriate alkylating agent or sulfonating agent. An appropriate alkylating agent or sulfonating agent is one that transfers an R group as desired in the final product of formula I. Appropriate
20 alkylating agents are RX_1 in which R is an C_1 - C_6 alkyl or substituted C_1 - C_6 alkyl as desired and X_1 is a leaving group, such as bromo, chloro, iodo, or tosylate. Appropriate sulfonating agents are $R'SO_2X_2$ in which transfers a sulfonyl containing R as desired and X_2 is a leaving group, typically
25 chloro, fluoro, or another group $R'SO_2O-$ to form the anhydride of the sulfonating agent. Such reactions are carried out in a suitable solvent such as dimethyl sulfoxide, acetonitrile, dimethylformamide, or tetrahydrofuran at temperatures of from about -20°C to
30 ambient temperature. The reaction is carried out using an appropriate base such as sodium hydride or potassium hydride and may advantageously use a catalyst such as, 18-crown-6 ether. Generally, 1-4 equivalents of an appropriate alkylating agent or sulfonating agent are used. The reaction
35 typically requires 1 to 18 hours. The product can be isolated and purified by techniques well known in the art, such as quenching, filtration, extraction, evaporation,

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trituration precipitation, chromatography, and recrystallization.

5 In Scheme A, step c, a 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole of formula (3) or a 3-(piperidin-4-yl)-1H-indole of formula (4) is deprotected to give a compound of formula (5). The removal of suitable protecting groups is well known and appreciated in the art (Protecting Groups in Organic Synthesis, Theodora Greene (Wiley-Interscience)).

10 In Scheme A, step d, a compound of formula (5) is contacted with an appropriate sulfonating agent of formula (6) to give a compound of formula I. An appropriate sulfonating agent of formula (6) is one in which X is, or gives rise to X, a desired in the compound of formula I and X₃ is a leaving group, typically fluoro or chloro, or is the anhydride of the sulfonating agent of formula (6). As one
15 the possible variations mentioned above, the skilled person will appreciate that unprotected compounds, that is, indoles of formula (1) having a 5-hydroxy, may undergo sulfonation as described in Scheme A, step d, and subsequently undergo
20 the chemistry of Scheme A, step a, to give a compound of formula I.

For example, a compound of formula (5) is contacted with from 1-10 equivalents of an appropriate sulfonating agent of formula (6). The reaction is generally carried out
25 in a solvent such as dimethyl sulfoxide, acetonitrile, dimethylformamide, water, or tetrahydrofuran at temperatures of from about -20°C to ambient temperature. The reaction is carried out using an appropriate base such as sodium
30 hydride, potassium hydride, sodium hydroxide, or potassium hydroxide. The reaction typically requires 1 to 18 hours. The product can be isolated and purified by techniques well known in the art, such as quenching, filtration, extraction, evaporation, trituration, precipitation, chromatography, and recrystallization.

35 Alternately, a compound of formula (5) is contacted with from 1-10 equivalents of an appropriate sulfonating agent of formula (6) in a solvent such as dimethyl

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sulfoxide, acetonitrile, dimethylformamide, or tetrahydrofuran. An organic base is added such as, triethylamine, collidines, pyridine, or lutidines. The compounds of formulas (5) and (6) are generally stirred at room temperature and the organic base is added dropwise. When carried out with an organic base, the reaction typically requires 48 to 72 hours. The product can be isolated and purified by techniques described above.

The compound of formula I thus obtained can be further elaborated, if desired. For example, when step d is carried out using a compound of formula (6) in which X is nitro the compound of formula I, can be reduced by hydrogenation over 5% palladium on carbon in an appropriate solvent such as ethanol at atmospheric pressure to give the compound of formula I in which X is amino. The amino group can be further elaborated, as is well known in the art, by sulfonation to give further compounds of formula I. Also, a compound in which R₄ is halo, in particular bromo can undergo a variety of coupling reactions to give compounds in which R₄ is vinyl, allyl, or C₂-C₆ alkynyl.

Scheme A, optional step e, not shown, an acid addition salt of a compound of formula I is formed using a pharmaceutically-acceptable acid. The formation of acid addition salts is well known and appreciated in the art.

The present invention is further illustrated by the following examples and preparations. These examples and preparations are illustrative only and are not intended to limit the invention in any way.

The terms used in the examples and preparations have their normal meanings unless otherwise designated. For example, "°C" refers to degrees Celsius; "N" refers to normal or normality; "M" refers to molar or molarity; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "mL" refers milliliter or milliliters; "mp" refers to melting point; "brine" refers to a saturated aqueous sodium chloride solution; etc. In the ¹H NMR, all chemical shifts are given in δ, unless otherwise indicated.

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Preparation 15-Methoxy-7-methyl-1H-indole

To a solution of 4-methoxy-2-methylaniline (0.36 mole, 50.0 g) in methylene chloride (450 mL) cooled to 10 °C (acetone/ice) was added a solution of 1.0M boron trichloride in methylene chloride (0.50 mole, 500 mL) while maintaining the reaction temperature below -10 °C. Chloroacetonitrile (1.82 mole, 137.6 g) was added to the reaction while maintaining the internal temperature below 0°C. This was followed by the addition of diethylaluminum chloride (0.40 mole, 48.34 g, 50 mL) while maintaining the reaction temperature below 0 °C. The solution was then refluxed for 5.25 hours. The reaction was cooled to room temperature and carefully treated with 5N hydrochloric acid (0.450 L) and water (1 L). The suspension was heated to reflux and cooled to room temperature. The phases were separated and the aqueous phase was extracted with methylene chloride (3 x 500 mL). The combined organic phases were filtered through a pad of silica (height of silica = 8 cm) in a scintered glass funnel (inner diameter of funnel = 12 cm). Material eluted from silica pad with methylene chloride (3 x 500 mL) to afford 1-(2-amino-5-methoxy-3-methylphenyl)-2-chloroethanone plus chloroacetonitrile. The mixture was concentrated *in vacuo* to afford 40.1 g (51%) 1-(2-amino-5-methoxy-3-methylphenyl)-2-chloroethanone that slowly crystallized. A solution of 1-(2-amino-5-methoxy-3-methylphenyl)-2-chloroethanone (0.19 mole, 40.1 g) in 9:1 dioxane:water (935 mL) was added sodium borohydride (0.19 mole, 7.1 g). The reaction was stirred one hour at room temperature refluxed for 4.5 hours. The reaction was cooled to room temperature and treated with 1N hydrochloric acid (310 mL). This mixture was heated to 80 °C and cooled to room temperature. The reaction was treated with water (500 mL), extracted with ethyl acetate (3 x 500 mL) and the organic phases were combined, concentrated *in vacuo* to afford an oil. The oil was dissolved in methylene chloride

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and filtered through a pad of silica (height of silica = 10 cm) in a scinter glass funnel (inner diameter of funnel = 14.5 cm). Material eluted with methylene chloride. Fractions containing the title compound were combined, concentrated in vacuo to afford 23.32g (77%) of the title compound as an oil: mass spectrum (ion spray): m/z =161(M); ^1H NMR(DMSO- d_6): 7.25 (t, J = 2.93Hz, 1H), 6.84 (d, J =2.20Hz, 1H), 6.53 (d, J =1.46Hz, 1H), 6.32 (dd, J =2.93, 1.83Hz, 1H), 3.71 (s, 3H), 2.41 (s, 3H).

10

Preparation 2

5-Methoxy-6-fluoro-1H-indole

Fuming nitric acid (24 mL) was dissolved in concentrated H_2SO_4 in a round bottom flask. 3,4-Difluorobromobenzene (20 g, 104 mmol) was added dropwise via pipette with vigorous stirring. After addition was complete, the reaction was allowed to stir at room temperature for 2 hours. The reaction was poured into ice water and extracted 2x250 mL with Et_2O . The organic layers were collected, combined, dried over MgSO_4 , filtered, and the solvent removed leaving a light yellow oil (24.02 g, 97% yield) of 1-bromo-4,5-difluoro-2-nitro-benzene.

1-Bromo-4,5-difluoro-2-nitro-benzene (24 g, 100 mmol) was carefully added dropwise to a solution of sodium methoxide (1.2 eq) in MeOH. After addition was complete, the reaction was stirred at room temperature for 2.5 hours. The solvent was removed in vacuo and the residue diluted with water and extracted 2 x 250 mL with Et_2O . The organic layers were combined, dried over MgSO_4 , filtered, and the solvent removed in vacuo leaving a yellow solid of 1-bromo-4-fluoro-5-methoxy-2-nitro-benzene: ^1H NMR (300 MHz, CDCl_3) 3.99 (s, 3H), 7.26 (m, 1H), 7.83 (d, 1H). MS(FD+): m/z 249, 251 (M+). Calculated for $\text{C}_7\text{H}_5\text{BrFNO}_3$: C, 33.63; H, 2.02; N, 5.60; found: C, 33.79; H, 1.98; N, 5.62. 1-Bromo-4-fluoro-5-methoxy-2-nitro-benzene (20.5 g, 82 mmol) was hydrogenated over Pt on C (sulfided) at 60 psi (413 kPa) in THF (600 mL) for 4 hours. The reaction was filtered through celite to

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remove the catalyst. Removal of the solvent left a brown solid of 2-bromo-5-fluoro-4-methoxy-phenylamine which was taken on without further purification. 2-Bromo-5-fluoro-4-methoxy-phenylamine (18 g, 81.8 mmol) was dissolved in pyridine (200 mL) in a 500 mL round bottom flask equipped with a stir bar, septum, pressure equalizing dropping funnel, and nitrogen line with bubbler. The solution was cooled in an ice bath and ethyl chloroformate (1.5 eq., 122.7 mmol) was added dropwise from the dropping funnel. After addition was complete, the reaction was allowed to stir overnight gradually warming to room temperature. The pyridine was removed leaving a brown residue. This residue was taken up in Et₂O/water and transferred to a separatory funnel. The water was extracted with Et₂O (2 X 300 mL). The organic layers were combined, dried over MgSO₄, filtered, concentrated in vacuo to obtain a 23.62 g (99%) of a brown solid: ¹H NMR (300 MHz, CDCl₃, 1.33 (t, 3H), 3.85 (s, 3H), 4.23 (q, 2H), 7.09 (d, 1H), 7.97 (bd, 1H); MS(FD+): m/z 291, 293 (M+).

(2-Bromo-5-fluoro-4-methoxy-phenyl)-carbamic acid ethyl ester (23 g, 78.74 mmol) was converted to the ethynyl compound following a similar example in *J.Org.Chem.* 199, 62, 6507. The compound was purified by absorbing to silica gel and loading onto a pad of silica and using 7.5% EtOAc in hexanes as the mobile phase. Fractions containing the product were pooled and the solvent removed in vacuo leaving a yellow solid: mass spectra(ES+): m/z 310 (M+H)⁺; (ES-): m/z 308 (M-H)⁻.

A solution of sodium ethoxide (formed by dissolving NaH 11.45 g, 60% in oil, 286.2 mmol, 4 eq.) in ethanol was poured into an EtOH solution of (5-fluoro-4-methoxy-2-trimethylsilanylethynyl-phenyl)-carbamic acid ethyl ester (22.14 g, 71.55 mmol) in EtOH (250 mL). The reaction was allowed to stir at room temperature for 2 hours and heated to 75 °C overnight. The EtOH was removed in vacuo and the residue diluted with water. The aqueous suspension was extracted 2 x 300 mL with Et₂O. The organics were combined

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and washed with brine. The organic layer was collected, dried over MgSO_4 , filtered, and the solvent removed in vacuo leaving a dark red oil. The oil was purified by silica gel flash column chromatography using 15% EtOAc in hexanes as the mobile phase. Removal of the solvent in vacuo from the fractions containing the product left a golden yellow oil which solidified on standing: ^1H NMR (300MHz, CDCl_3): 3.93 (s, 3H), 6.48 (m, 1H), 7.15 (m, 3H), 8.11 (bs, 1H); MS(ES+): m/z 166 (M+H) $^+$; MS(ES-): m/z 164 (M-H) $^-$;
10 Calculated for $\text{C}_9\text{H}_8\text{FNO}$: C, 65.45; H, 4.88; N, 8.48; found: C, 65.17; H, 4.97; N, 8.70.

Preparation 3

15 3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-5-hydroxy-1H-indole

To a solution of 1H-indol-5-ol (18.60 g, 0.14 mol) in methanol (250 mL), stirring at room temperature under nitrogen, was slowly added potassium hydroxide (31.4 g, 0.56 mol) in methanol (100 mL). 1-methyl-4-piperidone (29.0 mL, 20 0.24 mol) was added dropwise to the black solution. The reaction mixture was heated at 70 °C for 8 hours, cooled to room temperature, concentrated in vacuo. The resulting residue was directly purified on silica gel. Elution with a 9:1 mixture of dichloromethane and 7 N ammonia in methanol
25 provided 21.25 g (62%) of the title compound as a tan solid: mp=182-185°C; ^1H NMR (400 MHz, $\text{dmsO}-d_6$): 10.78 (br s, 1H), 8.64 (s, 1H), 7.22 (d, 1H, $J = 2.4$ Hz), 7.13 (d, 1H, $J = 8.8$ Hz), 7.10 (d, 1H, $J = 1.6$ Hz), 6.59 (dd, 1H, $J = 8.8, 1.2$ Hz), 5.94 (br s, 1H), 3.02-2.98 (m, 2H), 2.52 (br t, 2H, $J =$
30 5.6 Hz), 2.48-2.42 (m, 2H), 2.24 (s, 3H); MS (APCI): m/e 229.1 (M+1).

Preparation 4

35 5-Benzyloxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of potassium hydroxide (22 g, 392 mmol) in methanol (160 mL) was added 5-benzyloxyindole (24.7 g,

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111 mmol) followed by 1-methyl-4-piperidone (17.7 mL, 144 mmol) and methanol (80 mL). The reaction mixture was stirred at reflux for 18h, cooled to ambient temperature and filtered. The precipitate was washed with methanol and dried under vacuum to give 31.7 g (90%) of the title compound: mp=197-199 °C dec; MS(m/e): 318 (M⁺). Calculated for C₂₁H₂₂N₂O: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.24; H, 6.99; N, 8.85.

10

Preparation 56-Fluoro-5-methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

By a method similar Preparation 3 using 1-methyl-4-piperidone (18.7mmole, 2.11g), potassium hydroxide (62.3mmole, 3.49g) 6-fluoro-5-methoxy-1H-indole (17.8mmole, 2.94g) to afford 4.11g (88%) of the title compound: Mass spectrum (ion spray): m/z =261(M+1); ¹H NMR(DMSO-d₆): 7.37 (d, 1H), 7.32 (d, 1H), 7.19 (d, 1H), 6.09 (t, 1H), 3.86 (s, 3H), 3.05 (d, 2H), 2.51 (m, 2H), 2.49 (m, 2H), 2.29 (s, 3H); Calculated for C₁₅H₁₇FN₂O: C, 69.21; H, 6.58; N, 10.76. Found: C, 69.14; H, 6.59; N, 10.72.

Preparation 65-Methoxy-7-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

By a method similar to Preparation 3, using 5-methoxy-7-methyl-1H-indole (0.12mole, 20.02g), methanol (240 mL), potassium hydroxide (0.43mole, 24.39g) and 1-methyl-4-piperidone (0.13mole, 14.76g) afforded 24.72 (78%) of the title compound: Mass spectrum (ion spray): m/z =(ES+) 257(M+1), (ES-) 255(M-1); ¹H NMR(DMSO-d₆): 7.32 (s, 1H), 7.06 (1H), 6.59 (1H), 6.05 (m, 1H), 3.75 (s, 3H), 3.04 (2H), 2.50 (m, 4H), 2.42 (s, 3H), 2.29 (s, 3H).

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Preparation 77-Methoxy-9-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole

5 To a solution of 7-methoxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole (718 mg, 3.83 mmol) (Clark, R.D.; Muchowski, J.M.; Fisher, L.E.; Flippen, L.A.; Repke, D. B.; Souchet, M. *Synthesis* 10,871-878(1991); Ishikura, M.; Terashima, M. *Tetrahedron Lett.* 33, 6849-6852(1992)) in glacial AcOH (20
10 mL) at 60°C was added H₃PO₄ (5.0 mL, 10 mmol, 2.0 N) and 1-methyl-4-piperidone (1.2 mL, 11.5 mmol). The reaction was heated for 1h at 60 °C, cooled to room temperature and poured into a mixture of ammonium hydroxide in ice water. This reaction mixture was extracted with ethyl acetate and
15 washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure yielded 1.07 g (99%) of the title compound as a brown oil: MS (ES+): m/e 283.0 (M+1).

Preparation 87-Methyl-3-(1-methylpiperidin-4-yl)-1H-indole-5-ol

20 In a round bottom flask was placed 5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (3.9 mmole, 1.01 g) and pyridine hydrochloride (25 g). The flask was then placed in
25 a preheated oil bath set at 190 °C for 45 minutes. This solution was cooled to room temperature. The resulting solidified material was dissolved in water (200 mL). The pH was adjusted to approximately 10.3, which resulted in a precipitate. The insoluble material was collected by
30 filtration, rinsed with water to afford 0.781g (82%) of the title compound: mass spectrum (ion spray): m/z =245(M+1); ¹H NMR(DMSO-d₆): 10.40 (s, 1H), 8.45 (s, 1H), 6.93 (s, 1H), 6.68 (s, 1H), 6.40 (s, 1H), 2.90 (m, 2H), 2.60 (m, 1H), 2.36 (s, 3H), 2.26 (s, 3H), 2.08 (m, 2H), 1.90 (m, 2H), 1.70 (m, 2H);
35 Calculated for C₁₅H₂₀N₂O: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.76; H, 8.15; N, 11.71.

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Preparation 92-Methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole hydrochloride

By a method similar to Preparation 8, using 2-methyl-5-methoxy-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (258 mg, 1.0 mmol) and 25 g of pyridine hydrochloride gave the crude product. Flash chromatography [silica gel, dichloromethane/2N NH₃ (methanol) (90/10)] gave 244 mg (100%) of the final product as a colorless oil. Formation of the hydrochloride salt in Et₂O provided a white solid: mp=175 °C; MS(m/e): 245 (M+1); Calculated for C₁₅H₂₀N₂O·HCl·0.3 Et₂O·0.3H₂O: C, 63.08; H, 8.04; N, 9.08. Found: C, 62.97; H, 8.11; N, 8.69.

Preparation 107-Methyl-3-(1-methylpiperidin-4-yl)-1-phenethyl-1H-indol-5-ol

By a method similar to Preparation 8, using 5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1-phenethyl-1H-indole (0.288 g) and pyridine hydrochloride (25 g) to afford 0.143 (52%) of the title compound: mass spectrum (ion spray): m/z = 349 (M+1); Calculated for C₂₃H₂₈N₂O·0.3H₂O: C, 78.06; H, 8.15; N, 7.92. Found: C, 78.24; H, 8.18; N, 8.11.

Preparation 116-Fluoro-3-(1-methylpiperidin-4-yl)-1H-indole-5-ol

By a method similar to Preparation 8, using 6-fluoro-5-methoxy-3-(1-methylpiperidin-4-yl)-1H-indole (0.410 g) and 25 g of pyridine hydrochloride gave 0.360g (93%) the title compound: Mass spectrum (ion spray): m/z =248 (M).

Preparation 121-Benzyl-7-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole

By a method similar to Preparation 8, using 1-benzyl-5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (1.62 g) and pyridine hydrochloride (25 g) to afford 0.936 g (60%)

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of the title compound: Mass spectrum (ion spray): $m/z = 335$ (M+1).

Preparation 13

5 1-Propyl-7-methyl-3-(1-methylpiperdin-4-yl)-5-hydroxy-1H-indole

By a method similar to Preparation 8, using 1-propyl-5-methoxy-7-methyl-3-(1-methylpiperdin-4-yl)-1H-indole (1.24 g) and pyridine hydrochloride (25 g) to afford 1.03 g
10 (87%) of the title compound: mass spectrum (ion spray): $m/z = 287$ (M+1); Calculated for $C_{18}H_{26}N_2O \cdot 0.4 H_2O$: C, 73.63; H, 9.34; N, 9.23. Found: C, 73.70; H, 9.34; N, 9.33.

Preparation 14

15 1-Ethyl-7-methyl-3-(1-methylpiperdin-4-yl)-5-hydroxy-1H-indole

By a method similar to Preparation 8, using 1-ethyl-5-methoxy-7-methyl-3-(1-methylpiperdin-4-yl)-1H-indole (1.13 g) pyridine hydrochloride (25 g) to afford 0.996 g (93%) of the
20 title compound: mass spectrum (ion spray): $m/z = 273$ (M+1); Calculated for $C_{17}H_{24}N_2O \cdot 0.6 H_2O$: C, 72.10; H, 8.97; N, 9.89. Found: C, 72.09; H, 8.97; N, 9.85.

Preparation 15

25 1,7-Dimethyl-3-(1-methylpiperdin-4-yl)-5-hydroxy-1H-indole

By a method similar to Preparation 8, using 5-methoxy-1,7 dimethyl-3-(1-methylpiperdin-4-yl)-1H-indole (1.53 g) and pyridine hydrochloride (25 g) to afford 1.33 g (92%) of the title compound: mass spectrum (ion spray): $m/z =$
30 259 (M+1); 1H NMR ($DMSO-d_6$): 8.47 (s, 1H), 6.81 (s, 1H), 6.62 (d, $J=2.20$ Hz, 1H), 6.33 (d, $J=1.46$ Hz, 1H), 3.88 (s, 3H), 2.82 (m, 2H), 2.53-2.46 (m, 4H), 2.19 (s, 3H), 1.99 (m, 2H), 1.84 (m, 2H), 1.64 (m, 1H), 1.56 (m, 1H); Calculated for $C_{16}H_{22}N_2O \cdot 0.6 H_2O$: C, 71.39; H, 8.69; N, 10.41. Found: C,
35 71.39; H, 8.31; N, 10.33.

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Preparation 169-(1-Methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-ol

5 7-Methoxy-9-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole (0.92 g, 3.23 mmol) was dissolved in HBr (8.0 mL, 49%) and heated within a range of 105-115 °C for 2.5 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between
10 CH₂Cl₂, IPA, and aq. K₂CO₃. The organic layer was washed with brine, dried (K₂CO₃), filtered, and reduced under pressure. The residue was purified by PCTLC (silica gel GF rotor; 95:5 CHCl₃:2M NH₃ in MeOH) to give 705 mg (81%) of a pale pink foam. The hydrochloride was formed in EtOAc to
15 give the title compound as a white solid: mp >250°C; MS (ES⁺): m/e 285.0 (M+1); Calculated for C₁₇H₂₂N₂O 1.1HCl: Calcd: C, 65.77; H, 7.50; N, 9.06. Found: C, 65.72; H, 7.53; N, 8.93.

20

Preparation 173-(1-Methylpiperidin-4-yl)-5-hydroxy-1H-indole

A mixture of 5-benzyloxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (16.4 g, 51.5 mmol) and 5% palladium on carbon (4.0 g) in ethanol (125 mL) and
25 tetrahydrofuran (125 mL) was hydrogenated with an initial hydrogen pressure of 60 psi (413 kPa) at ambient temperature for 16 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was crystallized from methanol and THF to give 6.06 g (51%) of
30 the title compound as white crystals: mp=234-237 °C; MS(m/e): 230 (M⁺); Calculated for C₁₄H₁₈N₂O: Calcd: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.79; H, 8.17; N, 12.33.

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Preparation 181-Methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole
oxalate hemihydrate

5 A mixture of 5-benzyloxy-1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (955 mg, 2.87 mmol) and 5% palladium on carbon (240 mg) in methanol (100 mL) was hydrogenated with an initial hydrogen pressure of 60 psi (413 kPa) at ambient temperature for 16 h. The reaction
10 mixture was filtered and concentrated under reduced pressure. The product was purified by flash chromatography (silica gel, 5% 2M ammonia in methanol/methylene chloride) to give 437 mg (62%) of homogeneous product as purple foam. The product was crystallized as the oxalic acid salt from
15 ethyl acetate to give the title compound as a white powder: mp=68-75 °C dec.; MS(m/e): 245 (M+1); Calculated for $C_{15}H_{20}N_2O \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 57.94; H, 6.86; N, 7.95. Found: C, 58.17; H, 6.53; N, 8.04.

20

Preparation 195-(t-Butyldimethylsilanyloxy)-3-(1-methylpiperidin-4-yl)-1H-indol

To a solution of 3-(1-methyl-pyridin-4-yl)-5-hydroxy-1H-indole (8.0 g, 34.7 mmol) and 1-methyl-2-pyrrolidinone
25 (10 mL) in dichloromethane (90 mL) stirring at 0 °C, was added tert-butyldimethylsilyl chloride in small portions (5.50 g, 36.5 mmol), followed by imidazole also in small portions (2.48 g, 36.5 mmol). The reaction mixture was stirred for 1 hour at 0 °C, then overnight at room
30 temperature. The mixture was concentrated in vacuo to a solid residue, which was directly purified on silica gel. Elution with a 9:1 mixture of dichloromethane and methanol provided 7.60 g (63%) of the title compound as a white solid: mp=191-195°C; 1H NMR (400 MHz, $dmsO-d_6$): 10.46 (s, 1H), 7.02 (d, 1H, $J = 8.4$ Hz), 6.87 (d, 1H, $J = 2.4$ Hz), 6.74 (d, 1H, $J = 2.4$ Hz), 6.45 (dd, 1H, $J = 8.6, 2.6$ Hz), 2.69 (br d, 2H, $J = 11.2$ Hz), 2.46 (tt, 1H, $J = 11.8, 3.6$

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Hz), 2.04 (s, 3H), 1.92-1.80 (m, 2H), 1.75-1.67 (m, 2H), 1.50 (qd, 2H, $J = 12.4, 3.6$ Hz), 0.81 (s, 9H), 0.00 (s, 6H); MS (APCI): m/e 345.2 (M+1).

5

Preparation 207-Methoxy-9-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrole[1,2-a]indole

To a solution of 7-methoxy-9-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole (1.07 g, 3.79 mmol) in CH_2Cl_2 (20 mL) was slowly added trifluoroacetic acid added. The clear solution was then cooled to 0 °C and Et_3SiH (0.61 mL, 3.79 mmol) was added dropwise. The reaction mixture was then allowed to stir for an additional 2 h at 0 °C. The solution was concentrated under reduced pressure, dissolved in tartaric acid, washed with hexanes, basified (K_2CO_3), and extracted with CH_2Cl_2 . The organic layer was dried (K_2CO_3), concentrated under reduced pressure, and purified by PCTLC (silica gel GF rotor; 95:5 CHCl_3 :2M NH_3 in MeOH) to give 1.05 g (97%) of a yellowish foam: MS (ES+): m/e 285.0 (M+1).

Preparation 213-(1-Methylpiperidin-4-yl)-5-hydroxy-1H-indole

By a method similar to Preparation 20, using 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5-hydroxy-1H-indole (1.25g, 5.47 mmol) in dichloromethane (5 mL) trifluoroacetic acid (5 mL), triethylsilane (875 mL, 6.0 mmol) afforded 1.14 g (90%) of the title compound as a tan solid: mp=233-237 °C; ^1H NMR (400 MHz, $\text{dmsO}-d_6$): 10.41 (br s, 1H), 8.52 (br s, 1H), 7.08 (d, 1H, $J = 8.0$ Hz), 6.92 (d, 1H, $J = 2.0$ Hz), 6.80 (d, 1H, $J = 2.0$ Hz), 6.53 (dd, 1H, $J = 8.4, 2.0$ Hz), 2.84 (br d, 2H, $J = 11.2$ Hz), 2.63-2.50 (m, 1H), 2.19 (s, 3H), 2.08-1.97 (m, 2H), 1.85 (br d, 2H, $J = 12.0$ Hz), 1.72-1.57 (m 2H); MS (ES+) m/e 231.0 (M+1).

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Preparation 225-Benzoyloxy-3-(1-methylpiperidin-4-yl)-1H-indole

By a method similar to Preparation 20, using
5 trifluoroacetic acid (1.6 mL), 5-benzoyloxy-3-(1-methyl
-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (222 mg, 0.7
mmol), methylene chloride (3 mL) and triethylsilane (111 μ L,
0.7 mmol) gave the title compound as a yellow foam (210 mg)
which was crystallized from ethyl acetate to give 160 mg of
10 pale yellow crystals: mp=163-164 °C; MS(m/e): 321 (M+1), 379
(M+59); Calculated for $C_{21}H_{24}N_2O$: Calcd: C, 78.72; H, 7.55;
N, 8.74. Found: C, 78.63; H, 7.64; N, 8.78.

Preparation 2315 6-Fluoro-5-methoxy-3-(1-methylpiperidin-4-yl)-1H-indole

A suspension of 6-fluoro-5-methoxy-3-(1-methyl-1,2,3,6-
tetrahydropyridin-4-yl)-1H-indole (15.7 mmole, 4.09 g) in
tetrahydrofuran (30 mL) at room temperature was added sodium
borohydride (31.4 mmole, 1.19 g). To this suspension was
20 carefully added acetic acid (47.1 mmole, 2.83 g). Severe
frothing occurred during the addition. The reaction was
stirred at room temperature for 1.0 hours. To the heavy
suspension was added 5N hydrochloric acid (30 mL). The
resulting solution was stirred at room temperature for 1.0
25 hour. Reaction was reduced in volume, cooled to 0°C and the
pH was adjusted to >12 with 50% wt/wt sodium hydroxide. The
reaction was extracted with ethyl acetate (3 x 25 mL),
organic phases were combined, dried over sodium sulfate,
filtered and concentrated in vacuo to a solid. The resulting
30 material was subjected to Waters LC2000 normal phase
chromatography, eluting with a linear gradient of 0 to 10%
methanol containing 1% ammonium hydroxide:chloroform over a
thirty minute period collecting 150 mL fractions. Fractions
containing the title compound were combined, reduced in
35 volume and set aside. The resulting crystals were collected
by filtration to afford 2.30 g (82%) of the title compound:
mass spectrum (ion spray): m/z =263 (M+1); 1H NMR(DMSO-d₆):

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10.65 (s, 1H), 7.16 (d, 1H), 7.13 (d, 1H), 7.03 (d, 1H),
3.83 (s, 3H), 2.81 (m, 2H), 2.63 (m, 1H), 2.20 (s, 3H), 1.98
(m, 2H), 1.86 (m, 2H), 1.62 (m, 2H); Calculated for
C₁₅H₁₉FN₂O: C, 68.21; H, 7.33; N, 6.66. Found: C, 68.09; H,
5 6.95; N, 10.52.

Preparation 24

5-Methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole

To a suspension of 5-methoxy-7-methyl-3-(1-methyl-
10 1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (0.1 mole, 24.71
g) in tetrahydrofuran (295 mL) at room temperature was added
sodium borohydride (0.2 mole, 7.29 g). Trifluoroacetic acid
(0.3 mole, 32.97 g) was added over a 15 minute period. The
reaction was stirred at room temperature for 1.5 hours. To
15 the heavy suspension was added 5N hydrochloric acid (200
mL). The resulting solution was stirred at room temperature
for 1.5 hours. To the reaction was added ethyl acetate (500
mL) then the pH was adjusted to >12 with 50% wt/wt sodium
hydroxide. The phases were separated and the aqueous phase
20 was extracted with ethyl acetate (2 x 500 mL). The organic
phases were combined, dried over sodium sulfate then
filtered. The filtrate was filtered through a pad of silica
(height of silica = 7.0 cm) in a scinter glass funnel (inner
diameter of funnel = 14.5 cm). After the first fraction was
25 collected the next two fractions were eluted with chloroform
(1.2 L each). The remaining fractions were eluted with
90:10:1 chloroform:methanol:ammonium hydroxide (1.2 L
fractions collected). The desired fractions were combined
and concentrated *in vacuo* to afford 18.94 g (76%) of the
30 title compound as a white solid: mass spectrum (ion spray):
m/z =259(M+1); ¹H NMR(DMSO-d₆): 7.02 (d, 1H), 6.81 (d, 1H),
6.53 (d, 1H), 3.74 (s, 3H), 2.84 (m, 2H), 2.62 (m, 1H), 2.39
(s, 3H), 2.23 (s, 3H), 2.06 (m, 2H), 1.90 (m, 2H), 1.67 (m,
2H).

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Preparation 255-Methoxy-2-methyl-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride

5 5-Methoxy-2-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (JOC 40, 2525 (1975), (6.1 g, 23.8 mmol) was reacted with hydrogen gas in the presence of Pt₂O (40 °C/18 h/60 psi (413 kPa)) in an ethanol solution. After filtering the catalyst, the ethanol was
10 evaporated to 5.92 g of solid foam. Flash chromatography [silica gel, dichloromethane /2N NH₃(methanol) (90/10)] gave 5.4 g (88%) of the final product as a light yellow solid. Formation of the hydrochloride salt in EtOAc/MeOH provided the title compound as a white solid: mp=241 °C; ms(m/e):
15 259 (M+1); Calculated for C₁₆H₂₂N₂O·HCl: C, 65.18; H, 7.86; N, 9.50. Found: C, 64.83; H, 7.54; N, 9.32.

Preparation 26

20 5-Benzyloxy-1-methyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole oxalate

To a solution of 5-benzyloxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole **1** (1.16 g, 3.64 mmol) in DMF (20 mL) was added sodium hydride (160 mg, 4.0 mmol, 60% dispersion in mineral oil). The reaction was cooled to 5°C
25 on an ice bath and methyl iodide (294 µL, 4.7 mmol) was added dropwise. The reaction mixture was stirred at 5 °C for 1 h, quenched with water, and extracted with ethyl acetate. The ethyl acetate extracts were washed with water, brine, dried (Na₂SO₄), filtered and concentrated under reduced
30 pressure to give 1.2 g of a yellow oil. The product was purified by flash chromatography (silica gel, 2% 2M ammonia in methanol/methylene chloride) to provide 1.0 g (83%) of green oil. The product was crystallized as the oxalic acid salt from ethyl acetate to give the title compound as a
35 yellow powder: mp=184-187 °C dec; ms(m/e): 333 (M+1); Calculated for C₂₂H₂₄N₂O·C₂H₂O₄: Calcd: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.20; H, 6.53; N, 6.35.

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Preparation 275-Methoxy-1,7-dimethyl-3-(1-methylpiperidin-4-yl)-1H-indole

By a method similar to Preparation 26, using 5-methoxy-
5 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (7.89 mmol,
2.04 g), iodomethane (7.89 mmol, 1.12 g, 0.491 mL), THF (140
mL), potassium hydride (7.89 mmol, 0.904 g), 18-crown-6
(0.79 mmol, 0.209 g) purification of the crude material was
by Waters LC2000 eluting with a linear gradient of 2 to 10%
10 2M ammonia in methanol:methylene chloride. Fractions
containing the title compound combined, concentrated in
vacuo to afford 1.55g (72%) of the title compound: mass
spectrum (ion spray): $m/z = 273 (M+1)$; 1H NMR (DMSO- d_6): 6.89
(s, 1H), 6.77 (d, $J=2.20Hz$, 1H), 6.47 (d, $J=1.46Hz$, 1H),
15 3.91 (s, 3H), 3.72 (s, 3H), 2.87-2.80 (m, 2H), 2.65-2.52 (m,
4H), 2.18 (s, 3H), 2.05-2.02 (m, 1H), 2.02-1.97 (m, 1H),
1.89-1.84 (m, 2H), 1.67-1.62 (m, 1H), 1.59-1.54 (m, 1H);
Calculated for $C_{17}H_{24}N_2O \cdot 0.1 H_2O$: C, 74.47; H, 8.90; N, 10.22.
Found: C, 74.13; H, 8.53; N, 10.25.

20

Preparation 285-Methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1-phenethyl-1H-indole

By a method similar to Preparation 26, using 5-methoxy-
25 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (5.81 mmol,
1.50 g), 35% potassium hydride (5.81 mmol, 0.665 g),
toluene-4-sulfonic acid phenethyl ester (5.81 mmole, 1.60
g), additional 18-crown-6 (5.22 mmol, 1.38 g) and additional
toluene-4-sulfonic acid phenethyl ester (2.90mmole, 0.802g)
30 were added to afford 0.31g (15%) of the title compound: mass
spectrum (ion spray): $m/z = 363 (M+1)$.

Preparation 291-Benzyl-5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole

By a method similar to Preparation 26, using 5-methoxy-
7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (5.81 mmol,
1.50g) and benzyl bromide (5.81mmol, 0.993g), THF (100 mL),

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35% potassium hydride (5.81 mmol, 0.665g), and 18-crown-6 (0.58 mmol, 0.153 g) afforded 1.63 g (81%) of the title compound: mass spectrum (ion spray): $m/z = 349(M+1)$:
Calculated for $C_{23}H_{28}N_2O \cdot 0.3H_2O$: C, 78.06; H, 8.15; N, 7.92.
5 Found: C, 78.13; H, 7.84; N, 8.03.

Preparation 30

1-Propyl-5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole

10 By a method similar to Preparation 26, using 5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (5.81mmole, 1.50g), iodopropane (5.81mmole, 0.987g, 0.566 mL) in THF (100mL), potassium hydride (5.81mmole, 0.665g), and 18-crown-6 (0.58mmole, 0.153g) afforded 1.26g (72%) of the
15 title compound: mass spectrum (ion spray): $m/z = 301(M+1)$; .
Calculated for $C_{19}H_{28}N_2O \cdot 0.3H_2O$: C, 74.61; H, 9.43; N, 9.16.
Found: C, 74.37; H, 9.03; N, 9.01.

Preparation 31

1-Ethyl-5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole

By a method similar to Preparation 26, using 5-methoxy-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (5.81mmole, 1.5g) in THF (100mL), 35% potassium hydride (5.81mmole, 0.665g), 18-crown-6 (0.58mmole, 0.153g), and iodoethane (5.81mmole, 0.906g, 0.464 mL) afforded 1.17g (70%) of the
25 title compound: mass spectrum (ion spray): $m/z = 287(M+1)$;
Calculated for $C_{18}H_{26}N_2O \cdot 0.1 H_2O$: C, 75.01; H, 9.16; N, 9.72.
Found: C, 75.10; H, 9.01; N, 9.79.

30

Preparation 32

1-phenethyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole

To solution of 5-(*t*-butyldimethylsilanyloxy)-3-(1-methylpiperidin-4-yl)-1H-indol (285 mg, 0.83 mmol) in
35 tetrahydrofuran (20 mL) stirring at 0 °C was treated with potassium hydride (99 mg of a 35% dispersion in oil, 0.87 mmol). The light yellow solution was stirred for 20 minutes

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at 0 °C. Phenethyl tosylate (2.29 g, 8.30 mmol) was added and stirred at 0 °C for 3h, and at room temperature overnight. Addition 35% potassium hydride (94 mg, 0.83 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was treated with tetrabutylammonium fluoride (830 µL of a 1M solution in tetrahydrofuran, 0.83 mmol) and was stirred overnight at room temperature, before concentrating *in vacuo*. Purification by silica gel chromatography 9:1 dichloromethane: methanol gave 175 mg (63%) of the title compound as orange foam: MS (APCI): m/e 335.2 (M+1).

Preparation 33

1-(4-Fluorobenzyl)-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole

By a method similar to Preparation 32, using 5-(*t*-butyldimethylsilyloxy)-3-(1-methylpiperidin-4-yl)-1H-indol (400 mg, 1.16 mmol), potassium hydride (139mg of a 35% dispersion oil, 1.21mmol) and 4-fluorobenzyl bromide (148 µL, 1.21 mmol), and chromatographic purification with a 9:1 mixture of dichloromethane and methanol provided 353 mg (90%) of the desired compound as an orange foam: ¹H NMR (dms_o-d₆): 8.61 (s, 1H), 7.25-7.00 (m, 6H), 6.82 (d, 1H, *J* = 2.0 Hz), 6.54 (dd, 1H, *J* = 8.8, 1.6 Hz), 5.20 (s, 2H), 2.84 (br d, 2H, *J* = 11.6 Hz), 2.62-2.50 (m, 1H), 2.19 (s, 3H), 2.01 (br t, 2H, *J* = 11.0 Hz), 1.85 (br d, 2H, *J* = 13.2 Hz), 1.62 (qd, 2H, *J* = 12.0, 2.4 Hz). MS (APCI): m/e 339.2 (M+1).

Preparation 34

1-Benzyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole

By a method similar to Preparation 32, using 5-(*t*-butyldimethylsilyloxy)-3-(1-methylpiperidin-4-yl)-1H-indol (350 mg, 1.02 mmol) in tetrahydrofuran (20 mL), potassium hydride (116 mg of a 35% dispersion in oil, 1.02 mmol) and benzyl bromide (121 µL, 1.02 mmol) and after stirring at room temperature overnight, the reaction mixture was

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directly treated with tetrabutyl ammonium fluoride (1.02 mL of a 1M solution in tetrahydrofuran, 1.02 mmol) and stirred at room temperature for three days. The solvent was then removed *in vacuo*, and the resulting residue was diluted with methanol (15 mL) and directly applied to a 5 g SCX column. After thoroughly washing with methanol, the column was eluted with a 8:2 mixture of dichloromethane and 2 N ammonia in methanol. The eluent was concentrated *in vacuo*, and the residue was further purified on silica gel. Elution with a 0% to 2% gradient of methanol in dichloromethane provided 323 mg (99%) of the title compound as an off-white gum: ^1H NMR (400 MHz, CDCl_3): 7.33-7.20 (m, 4H), 7.12-7.05 (m, 2H), 7.04 (d, 1H, $J = 8.4$ Hz), 6.82 (s, 1H), 6.70 (dd, 1H, $J = 8.6, 2.6$ Hz), 5.17 (s, 2H), 3.01 (br d, 2H, $J = 11.2$ Hz), 2.71 (tt, 1H, $J = 11.8, 4.0$ Hz), 2.38 (s, 3H), 2.22-1.98 (m, 4H), 1.98-1.88 (m, 2H): MS (ES+): m/e 321.0 (M+1).

Preparation 35

6-Methoxy-1,2,3,4-tetrahydroquinoline

6-Methoxyquinoline (48 g, 0.30 mol) was dissolved in 500 mL methanol and mix with PtO_2 (12 g, 52.8 mmol), the mixture was put in a Parr shaker heated to 40 °C under hydrogen (40 psi (275 kPa)) for 24h. The reaction was cool to room temperature, released the pressure, and then removed the catalyst. The solvent was concentrated resulting the title compound: ^1H NMR (300 MHz, CDCl_3) 1.90-1.97 (m, 2), 2.75 (t, 2H, $J = 6.4$ Hz), 3.25 (t, 2H, $J = 5.5$ Hz), 3.72 (s, 3H), 6.44-6.60 (m, 3H).

Preparation 36

8-Methoxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1,2-dione

A solution of 6-methoxy-1,2,3,4-tetrahydroquinoline (10 g, 61.3 mmol) 600 mL CH_2Cl_2 was slowly added to a solution of oxalyl chloride (8.4 mL, 94.5 mmol) in 100 mL CH_2Cl_2 at 0°C. After addition the reaction mixture was at 0 °C for 0.5h, aluminum chloride (24.5g, 184 mmol) was than added to the

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reaction mixture, the resulting mixture was warmed up to room temperature, stirred over night. The reaction mixture was poured on ice, diluted with 1N HCl, the aqueous layer was extracted with CHCl₃ (3 x 150 mL), the combined organic layers was washed with brine, dried over Na₂SO₄. The solvent was concentrated, the crude product was purified by flash chromatography (Hexane/ EtOAc), obtained 10.0 g (75%) of pure title compound: ¹H NMR (300 MHz, CDCl₃) 2.01-2.05 (m, 2H), 2.74 (t, 2H, J = 6.0 Hz), 3.73 (t, 2H, J = 5.8 Hz), 3.77 (s, 3H), 6.92-6.93 (m, 2H).

Preparation 37

8-Methoxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline

8-Methoxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1,2-dione (3.0 g, 13.8 mmol), was added to BH₃-THF (1.0 M, 30 mL, 30 mmol) dropwise at 0 °C. After addition the reaction mixture was stirred 0 °C for 5 h, then warmed to room temperature and stirred for 12 h. The reaction was quenched by adding 5N HCl cautiously at 0 °C until no gas evolution to pH = 8. The reaction mixture was diluted with water, extracted with ether, the combined organic layers were washed with brine, dried over Na₂SO₄. The solvate was removed in vacuo and purified by flash chromatography using hexanes/ethyl acetate (9:1). After purification, 1.3 g (50%) of title compound was obtained: ¹H NMR (300 MHz, CDCl₃) 2.21-2.27 (m, 2H), 2.96 (t, 2H, J = 6.1 Hz), 3.83 (s, 3H), 4.13 (t, 2H, J = 5.8 Hz), 6.36 (d, 1H, J = 2.8 Hz), 6.62 (d, 1H, J = 1.4 Hz), 6.91 (d, 1H, J = 2.2 Hz), 7.05 (d, 1H, J = 2.7 Hz).

Preparation 38

8-Methoxy-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline

By a method similar to Preparation 11, using 8-methoxy-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline (0.28g, 1.5 mmol), and N-methylpiperidone (Aldrich, 0.68g, 6.0 mmol) 0.12 g (27%) of title compound was obtained: ¹H NMR (300

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MHz, CDCl₃): 2.18-22.24 (m, 2H), 2.77 (s, 3H), 2.89-2.97 (m, 4H), 3.21 (t, 2H, *J* = 61 Hz), 3.68-3.49 (m, 2H), 3.85 (s, 3H), 4.10 (t, 2H, *J* = 5.7 Hz), 6.02 (m, 1H), 6.65-6.66 (m, 1H), 7.04-7.06 (m, 2H); MS (ELECTROSPRAY): *m/e* 283.0 (M+1).

5

Preparation 39

Benzenesulfonic acid 7-bromo-1H-indol-5-yl ester

Combine 3-bromo-4-nitrophenol (1 eq.), triethylamine (1.1 eq.) and tert-butyldimethylsilyl chloride (1.1 eq.) in methylene chloride at 0°C. After about 6 hours, pour the reaction mixture into ethyl acetate, wash with brine, dry the organic layer over Na₂SO₄ and then concentrate. Purify to give 3-bromo-4-nitro-1-tert-butyldimethylsilyloxybenzene.

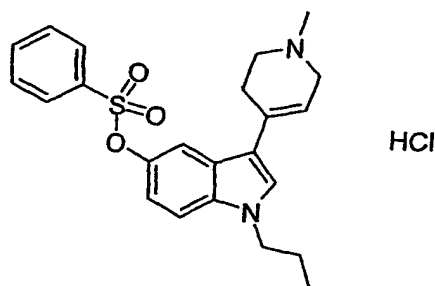
Combine 3-bromo-4-nitro-1-tert-butyldimethylsilyloxybenzene and dry THF. Cool to about -45°C and then treat with vinylmagnesium bromide (1.2 eq.) over a few minutes. After about 45 minutes, pour the reaction mixture into saturated aq. NH₄Cl, extract with ether, combined the organic extracts and extract with water, dry over Na₂SO₄ and concentrate. Purify to give 7-bromo-5-(tert-butyldimethylsilanyloxy)-1H-indole.

Combine 7-bromo-5-(tert-butyldimethylsilanyloxy)-1H-indole and methylene chloride and treat with tetrabutyl ammonium fluoride (1.0 eq.) at 0°C. After the mixture is stirred for about 1 hour, pour into ethyl acetate, wash with brine, dry the organic layer over Na₂SO₄ and concentrate. Purify to give 7-bromo-5-hydroxy-1H-indole.

Alternately, 7-bromo-5-hydroxy-1H-indole is prepared by the method of Kita et al, Heterocycles, 1992, 33 (2), 503-506).

Combine 7-bromo-5-hydroxy-1H-indole and 0.2 N NaOH (1.1 eq.) in THF. Cool to about 0°C before adding benzenesulfonyl chloride (1.10 eq.). Allow the reaction mixture to warm to ambient temperature. After 8 hours, pour into ethyl acetate, wash with water, dry the organic layer over Na₂SO₄ and concentrate. Purify to give the title compound.

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Example 1Benzenesulfonic acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1-propyl-1H-indol-5-yl ester hydrochloride

5

To a solution of benzenesulfonic acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester, from Example 46, (0.2 g, 0.54 mmol) in dimethylformamide (25 mL) at 0 °C under nitrogen was added sodium hydride in one portion (24.0 mg of a 60% dispersion in oil, 0.60 mmol). The light green mixture was stirred for 30 minutes at 0 °C and 1-propyl bromide (54 mL, 0.60 mmol) was added. After completion of the reaction, the reaction was quenched with water, extracted with ethyl acetate (2 x 125 mL), dried over magnesium sulfate, filtered, concentrated *in vacuo* to a residue that was purified on silica gel using 9:1 dichloromethane:methanol as the solvent to afford 58 mg (59%) of the title compound as an orange oil. The oil was dissolved in methanol (10 mL) and treated with ammonium chloride (11.8 mg, 0.22 mmol, dissolved in 10 mL methanol). The resulting solution was concentrated *in vacuo*, and triturated in a minimal amount of diethyl ether. Filtration and drying of the precipitate afforded 58 mg (59%) of the title compound as a yellow solid: mp=170-174 °C; MS (ES+): m/e 411.2 (M+1); ¹H NMR (400 MHz, CDCl₃): 7.86-7.78 (m, 2H), 7.66-7.58 (m, 1H), 7.52-7.44 (m, 2H), 7.27-7.40 (m, 1H), 7.13 (d, 1H, J = 8.8 Hz), 7.04 (s, 1H), 6.81 (dd, 1H, J = 8.8, 2.4 Hz), 5.71 (br s, 1H), 3.95 (t, 2H, J = 6.8 Hz), 3.08-3.03 (m, 2H), 2.63 (t, 2H, J = 6.0 Hz), 2.52-2.45 (m 2H), 2.38 (s, 3H), 1.78 (sextuplet, 2H, J = 7.2 Hz), 0.87

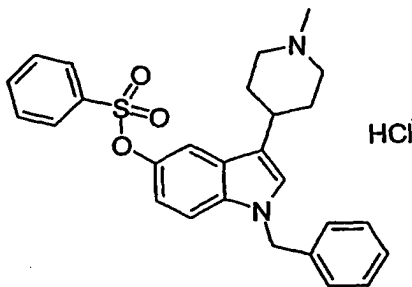
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-41-

(t, 3H, $J = 7.6$ Hz; Calculated for $C_{23}H_{26}N_2O_3S \cdot HCl \cdot 2.1H_2O$: C 56.93, H 5.56, N 5.77; Found: C 57.20, H 5.27, N 5.35.

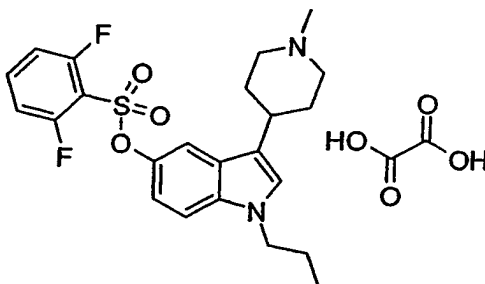
Example 2

5 Benzenesulfonic acid 1-benzyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from
10 Example 34 or 45, (200 mg, 0.54 mmol), benzyl bromide (64 μ L, 0.54 mmol) dimethylformamide (15 mL) and sodium hydride in one portion (22 mg of a 60% dispersion in oil, 0.54 mmol) gave 198 mg (80%) of the free base of the title compound as a gold-colored oil. The oil was dissolved in methanol (10
15 mL) and treated with ammonium chloride (46.0 mg, 0.86 mmol, dissolved in 10 mL methanol). The solution was concentrated in vacuo, and the resulting solid was triturated with a minimal amount of diethyl ether. Filtration and drying of the precipitate afforded 210 mg (98%) of the title
20 hydrochloride as an off-white solid: mp=227-230 °C; 1H NMR (400 MHz, $dms\text{-}d_6$): δ 10.41 (br s, 1H), 7.86-7.72 (m, 3H), 7.65-7.55 (m, 2H), 7.38 (s, 1H), 7.37 (d, 1H, $J = 8.8$ Hz), 7.30-7.10 (m, 6H), 6.68 (br d, 1H, $J = 8.8$ Hz), 5.31 (s, 2H), 3.42 (br d, 2H, $J = 11.6$ Hz), 3.10-2.95 (m, 2H), 2.94-
25 2.80 (m, 1H), 2.74 (s, 3H), 2.00-1.80 (m, 4H); MS (APCI): m/e 461.0 (M+1); Calculated (for $C_{27}H_{28}N_2O_3S \cdot HCl \cdot 0.6H_2O$): C 63.85, H 5.99, N 5.51, Cl 7.13; Found: C 63.96, H 5.78, N 5.59, Cl 7.11.

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Example 32,6-Difluorobenzenesulfonic acid 1-propyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5

By a method similar to Example 1, using 2,6-difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 42 or 47, (175 mg) dimethylformamide (25 mL), sodium hydride (19 mg of a 60% dispersion in oil, 0.47 mmol) and 1-bromopropane (43 mL, 0.47 mmol) gave 66 mg (34%) of the free base of the title compound as a gold oil. The oil was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (13.2 mg, 0.15 mmol, dissolved in 10 mL of ethyl acetate). An off-white precipitate formed immediately, which was filtered and dried to provide 70 mg (89%) of the title compound as an off white solid: mp=185-189 °C; MS (ES⁺): m/e 449 (M+1); ¹H NMR (400 MHz, dms^o-d₆): 7.94-7.82 (m, 1H), 7.43 (d, 1H, J = 8.8 Hz), 7.37 (t, 2H, J = 8.8 Hz), 7.29 (d, 1H, J = 2.4 Hz), 7.28 (s, 1H), 6.78 (dd, 1H, J = 9.0, 2.2 Hz), 4.03 (t, 2H, J = 7.2 Hz), 3.35 (br d, 2H, J = 12.0 Hz), 3.02-2.80 (m, 3H), 2.70 (s, 3H), 2.00-1.88 (m, 2H), 1.84-1.68 (m, 2H), 1.68 (sextuplet, 2H, J = 6.8 Hz), 0.77 (t, 3H, J = 6.8 Hz); Calculated (for C₂₃H₂₆F₂N₂O₃S•C₂H₂O₄): C 55.75, H 5.24, N 5.20; Found: C 55.63, H 5.17, N 5.13.

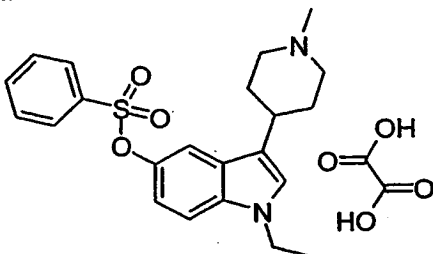
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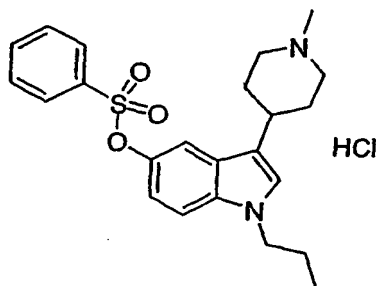
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Example 4Benzenesulfonic acid 1-ethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5 By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 34 or 45, (350 mg, 0.94 mmol), dimethylformamide (20 mL), sodium hydride (42 mg of a 60% dispersion in oil, 1.0 mmol) and ethyl iodide (76 mL, 0.94 mmol) provided 265 mg (70%) of the free base of the desired compound as a golden oil. The oil was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (59.8 mg, 0.66 mmol), dissolved in 10 mL of ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 235 mg (72%) of the title oxalate as an off-white solid: mp=127-130 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.84-7.74 (m, 3H), 7.66-7.58 (m, 2H), 7.37 (d, 1H, J = 8.8 Hz), 7.26 (s, 1H), 7.14 (d, 1H, J = 2.0 Hz), 6.68 (dd, 1H, J = 8.8, 2.4 Hz), 4.09 (q, 2H, J = 7.2 Hz), 3.39 (br d, 2H, J = 11.2 Hz), 2.98 (br t, 2H, J = 11.4 Hz), 2.90-2.78 (m, 1H), 2.73 (s, 3H), 1.98-1.88 (m, 2H), 1.84-1.70 (m, 2H), 1.27 (t, 3H, J = 7.2 Hz); MS (ES⁺): m/e 399.1 (M+1); Calculated (for C₂₂H₂₆N₂O₃S•C₂H₂O₄•0.6H₂O): C 57.72, H 5.89, N 5.60; Found: C 57.65, H 5.75, N 5.96.

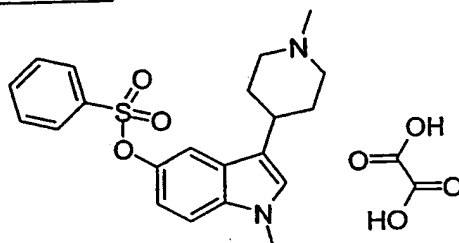
-44-

Example 5Benzenesulfonic acid 1-propyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methyl-pyridin-4-yl)-1H-indol-5-yl ester, from Example 34 or 45, (0.25 g, 0.67 mmol) in tetrahydrofuran (20 mL), sodium hydride (30.0 mg of a 60% dispersion in oil, 0.74 mmol), 1-propyl bromide (67 mL, 0.74 mmol) provided 182 mg (65%) of the desired benzenesulfonic acid 3-(1-methyl-pyridin-4-yl)-1-propyl-1H-indol-5-yl ester free base as a gold oil. The oil was dissolved in methanol (10 mL), treated with ammonium chloride (23.3 mg, 0.44 mmol), and dissolved in 10 mL methanol. The resulting solution was concentrated in vacuo, and triturated in a minimal amount of diethyl ether. Filtration followed by drying of the resulting precipitate afforded 180 mg (90%) of the title hydrochloride as a tan solid: mp=194-197 °C; MS (ES+) m/e 413.1 (M+1); ¹H NMR (400 MHz, dms_o-d₆): 7.84-7.74 (m, 3H), 7.66-7.58 (m, 2H), 7.36 (d, 1H, J = 8.8 Hz), 7.15 (br s, 1H), 6.90 (d, 1H, J = 2.0 Hz), 6.72 (dd, 1H, J = 8.8, 2.2 Hz), 3.99 (t, 2H, J = 7.0 Hz), 2.78 (br d, 2H, J = 11.6 Hz), 2.52-2.40 (m, 1H), 2.16 (s, 3H), 1.92 (br t, 2H, J = 10.8 Hz), 1.74-1.60 (m, 4H), 1.58-1.40 (m, 2H), 0.77 (t, 3H, J = 7.4 Hz); Calculated (for C₂₃H₂₈N₂O₃S•HCl•1.15H₂O): C 58.81, H 6.71, N 5.96; found: C 58.64, H 6.31, N 6.36.

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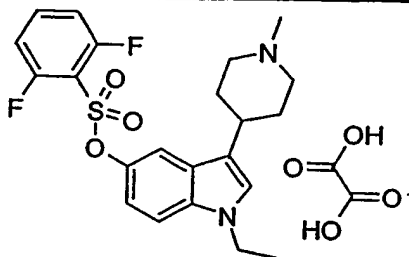
Example 6Benzenesulfonic acid 1-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 34 or 45, (300 mg, 0.81 mmol) in tetrahydrofuran (20 mL) potassium hydride (100 mg of a 35% dispersion in oil, 0.88 mmol), methyl iodide (50 mL, 0.81 mmol), 18-crown-6 ether (30 mg, 0.11 mmol) provided 246 mg (79%) of the free base of the desired product as an off-white gum. The gum was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (57.5 mg, 0.64 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 286 mg (94%) of the title oxalate as a white solid: mp=135-142 °C; ¹H NMR (400 MHz, dmsO-d₆): 7.82-7.73 (m, 3H), 7.65-7.57 (m, 2H), 7.31 (d, 1H, J = 8.8 Hz), 7.19 (br s, 1H), 7.14 (d, 1H, J = 2.0 Hz), 6.68 (dd, 1H, J = 8.8, 2.4 Hz), 3.67 (s, 3H), 3.39 (br d, 2H, J = 12.4 Hz), 2.98 (br t, 2H, J = 12.0 Hz), 2.91-2.79 (m, 1H), 2.73 (s, 3H), 1.98-1.86 (m, 2H), 1.84-1.68 (m, 2H). MS (ES⁺): m/e 385.0 (M+1); Calculated (for C₂₁H₂₄N₂O₃S•C₂H₂O₄•0.6H₂O): C 56.91, H 5.64, N 5.77; Found: C 56.89, H 5.32, N 5.42.

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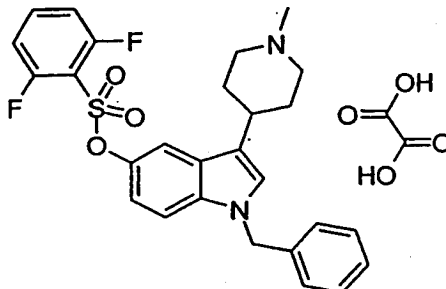
Example 72,6-Difluorobenzenesulfonic acid 1-ethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5

By a method similar to Example 1, using 2,6-difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 42 or 47, (425 mg, 1.05 mmol), tetrahydrofuran (20 mL), potassium hydride (120 mg of a 35% dispersion in oil, 1.05 mmol), ethyl iodide (84 mL, 1.05 mmol) and 18-crown-6 ether (40 mg, 0.15 mmol) provided 274 mg (60%) of the free base of the desired product as a colorless film. The film was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (17.1 mg, 0.63 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 297 mg (90%) of the title oxalate as an off-white solid: mp=161-165 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.93-7.83 (m, 1H), 7.43 (d, 1H, *J* = 9.6 Hz), 7.37 (t, 2H, *J* = 8.8 Hz), 7.29 (s, 1H), 7.28 (d, 1H, *J* = 2.4 Hz), 6.80 (dd, 1H, *J* = 8.8, 2.0 Hz), 4.10 (q, 2H, *J* = 7.2 Hz), 3.36 (br d, 2H, *J* = 11.6 Hz), 3.02-2.90 (m, 2H), 2.92-2.83 (m, 1H), 2.70 (s, 3H), 2.00-1.88 (m, 2H), 1.85-1.70 (m, 2H), 1.27 (t, 3H, *J* = 7.2 Hz). MS (ES⁺): *m/e* 435.1 (M+1); Calculated (for C₂₂H₂₄F₂N₂O₃S•0.9C₂H₂O₄•0.1H₂O): C 55.26, H 5.07, N 5.42; Found: C 55.44, H 4.94, N 5.50.

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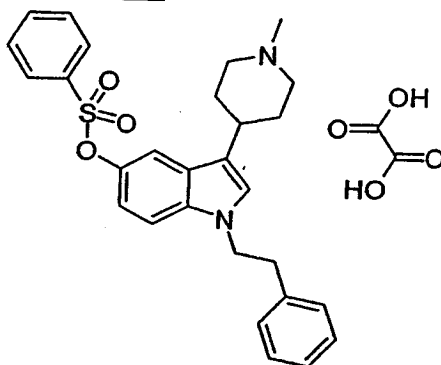
Example 82,6-Difluorobenzenesulfonic acid 1-benzyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5

By a method similar to Example 1, using 2,6-difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 42 or 47, (250 mg, 0.62 mmol), tetrahydrofuran (20 mL), potassium hydride (77 mg of a 35% dispersion in oil, 0.68 mmol) benzyl bromide (73 mL, 0.62 mmol) and 18-crown-6 ether (25 mg, 0.09 mmol) provided 100 mg (30%) of the free base of the desired product as a colorless film. The film was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (18.1 mg, 0.20 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 107 mg (90%) of the title oxalate as a tan solid: mp 205-208 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.92-7.82 (m, 1H), 7.47-7.30 (m, 5H), 7.30-7.10 (m, 5H), 6.77 (dd, 1H, J = 8.8, 1.6 Hz), 5.32 (s, 2H), 3.39 (br d, 2H, J = 12.0 Hz), 3.06-2.86 (m, 3H), 2.72 (s, 3H), 2.02-1.92 (m, 2H), 1.86-1.70 (m, 2H). MS (ES⁺): m/e 497.0 (M+1). MS (ES⁻): m/e 435.1 (M+1); Calculated (for C₂₇H₂₆F₂N₂O₃S•C₂H₂O₄): C 59.38, H 4.81, N 4.78; Found: C 59.03, H 4.93, N 4.55.

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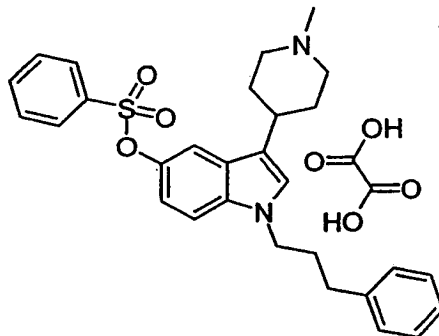
Example 9Benzenesulfonic acid 1-phenethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 42 or 47, (300 mg, 0.81 mmol), tetrahydrofuran (20 mL), potassium hydride (102 mg of a 35% dispersion in oil, 0.89 mmol) and toluene-4-sulfonic acid phenethyl ester (447 mg, 1.62 mmol) provided 132 mg (34%) of the free base of the desired product as a colorless oil. The oil was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (25.0 mg, 0.28 mmol, dissolved in 10 mL ethyl acetate upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 150 mg (96%) of the title oxalate as a white solid: mp=208-212 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.84-7.74 (m, 3H), 7.66-7.58 (m, 2H), 7.38 (d, 1H, *J* = 9.2 Hz), 7.24-7.08 (m, 7H), 6.65 (dd, 1H, *J* = 9.0, 2.2 Hz), 4.27 (t, 2H, *J* = 7.6 Hz), 3.42-3.30 (m, 2H), 3.04-2.88 (m, 4H), 2.88-2.76 (m, 1H), 2.71 (s, 3H), 1.94-1.83 (m, 2H), 1.80-1.63 (m, 2H); MS (ES⁺): *m/e* 475.1 (M+1); Calculated (for C₂₈H₃₀N₂O₃S•C₂H₂O₄•0.4H₂O): C 63.00, H 5.78, N 4.89; Found: C 63.09, H 5.64, N 4.86.

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Example 10

Benzenesulfonic acid 1-(3-phenylpropyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



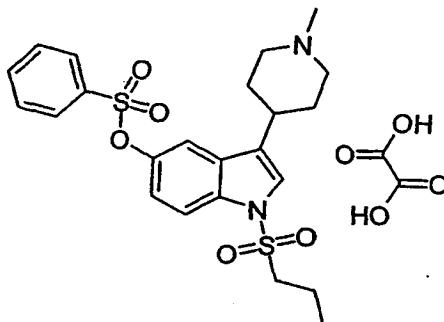
5 By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 34 or 45, (250 mg, 0.67 mmol), tetrahydrofuran (20 mL), potassium hydride (77 mg of a 35% dispersion in oil, 0.67 mmol), 1-bromo-3-phenylpropane (113 mL, 0.74 mmol)
10 provided 105 mg (32%) of the free base of the desired product as a colorless oil. The oil was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (19.3 mg, 0.21 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of
15 the precipitate provided 110 mg (88%) of the title oxalate as a white solid: mp=188-191 °C; ¹H NMR (400 MHz, dmsO-d₆): 7.84-7.74 (m, 3H), 7.62 (br t, 2H, J = 7.8 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.29-7.19 (m, 3H), 7.19-7.08 (m, 4H), 6.67 (dd, 1H, J = 8.8, 1.6 Hz), 4.08 (t, 2H, J = 7.4 Hz), 3.50-3.34
20 (m, 2H), 3.10-2.94 (m, 2H), 2.92-2.80 (m, 1H), 2.76 (s, 3H), 2.54-2.44 (m, 2H), 2.06-1.88 (m, 4H), 1.86-1.72 (m, 2H); MS (ES⁺): m/e 475.1 (M+1). MS (ES⁺): m/e 489.0 (M+1); Calculated (for C₂₉H₃₂N₂O₃S•C₂H₂O₄): C 64.34, H 5.92, N 4.84; found: C 64.23, H 5.78, N 5.01.

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Example 11

Benzenesulfonic acid 1-(propylsulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



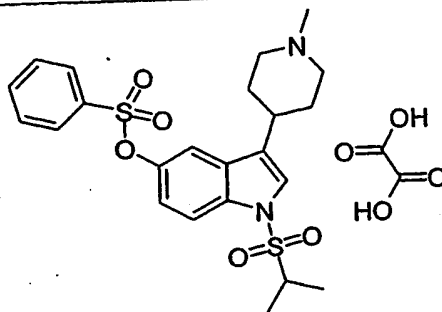
5 By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 34 or 45, (200 mg, 0.54 mmol), tetrahydrofuran (5 mL), potassium hydride (68 mg of a 35% dispersion in oil, 0.60 mmol) and 1-propanesulfonyl chloride (121 mL, 1.08 mmol) provided 67 mg (26%) of the free base of the desired compound as a tan gum. The gum was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (12.6 mg, 0.14 mmol, dissolved in 10 mL ethyl acetate), upon which formation of precipitate was observed. Filtration and drying of the precipitate afforded 72 mg (89%) of the title oxalate as a tan solid: mp=139-142 °C; ¹H NMR (400 MHz, dmsO-d₆): 7.88-7.73 (m, 4H), 7.63 (t, 2H, J = 7.8 Hz), 7.42 (s, 1H), 7.35 (d, 1H, J = 2.4 Hz), 6.98 (dd, 1H, J = 9.0, 2.2 Hz), 3.54 (t, 2H, J = 7.2 Hz), 3.38 (br d, 2H, J = 10.8 Hz), 3.04-2.84 (m, 3H), 2.72 (s, 3H), 2.00-1.88 (m 2H), 1.86-1.72 (m, 2H), 1.48 (sextuplet, 2H, J = 7.2 Hz), 0.80 (t, 3H, J = 7.2 Hz); MS (ES⁺): m/e 477.0 (M+1); Calculated (for C₂₃H₂₈N₂O₅S₂•C₂H₂O₄): C 52.99, H 5.34, N 4.94; found: C 53.20, H 5.33, N 4.89.

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Example 12

Benzenesulfonic acid 1-(isopropylsulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



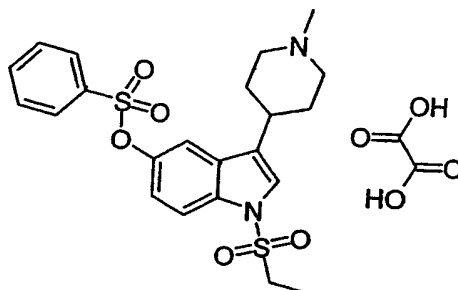
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By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 34 or 45, (200 mg, 0.54 mmol), tetrahydrofuran (5 mL), potassium hydride (68 mg of a 35% dispersion in oil, 0.60 mmol), isopropylsulfonyl chloride (121 mL, 1.08 mmol) provided 76 mg (30%) of the free base of the desired compound as a tan gum. This gum was converted to 82 mg (91%) of the title oxalate, isolated as a white solid: mp=134-138 °C. ¹H NMR (400 MHz, dmsO-d₆): 7.86-7.73 (m, 4H), 7.67-7.60 (m, 2H), 7.42 (s, 1H), 7.35 (d, 1H, *J* = 2.4 Hz), 6.97 (dd, 1H, *J* = 9.0, 2.2 Hz), 3.75 (septuplet, 1H, *J* = 7.2 Hz), 3.35 (br d, 2H, *J* = 12.4 Hz), 3.00-2.84 (m, 3H), 2.70 (s, 3H), 1.98-1.87 (m 2H), 1.87-1.70 (m, 2H), 1.13 (d, 6H, *J* = 6.8 Hz); MS (ES⁺): *m/e* 477.0 (M+1); Calculated (for C₂₃H₂₈N₂O₅S₂•C₂H₂O₄): C 52.99, H 5.34, N 4.94; found: C 53.16, H 5.20, N 4.86.

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Example 13

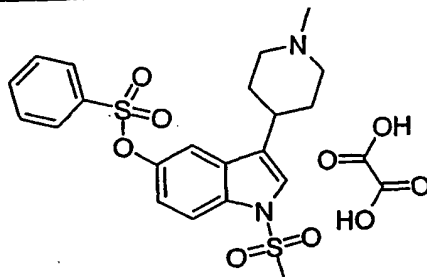
Example 13
Benzenesulfonic acid 1-ethylsulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from Example 34 or 45, (200 mg, 0.54 mmol), tetrahydrofuran (5 mL), potassium hydride (68 mg of a 35% dispersion in oil, 0.60 mmol), ethylsulfonyl chloride (102 mL, 1.08 mmol) provided 230 mg (92%) of the free base of the desired compound as a colorless gum. This gum was converted to 248 mg (90%) of the title oxalate, isolated as an off-white solid: mp 121-126 °C; ¹H NMR (400 MHz, dmsO-d₆): 7.88-7.73 (m, 4H), 7.64 (t, 2H, *J* = 7.8 Hz), 7.43 (s, 1H), 7.36 (d, 1H, *J* = 2.4 Hz), 6.98 (dd, 1H, *J* = 8.8, 2.4 Hz), 3.58 (q, 2H, *J* = 7.2 Hz), 3.38 (br d, 2H, *J* = 11.6 Hz), 3.04-2.86 (m, 3H), 2.72 (s, 3H), 2.00-1.90 (m 2H), 1.88-1.74 (m, 2H), 1.01 (t, 3H, *J* = 7.2 Hz). MS (ES⁺): *m/e* 463.0 (*M*+1); Calculated (for C₂₂H₂₆N₂O₅S₂•C₂H₂O₄): C 52.16, H 5.11, N 5.07; found: C 51.79, H 4.99, N 4.88.

-53-

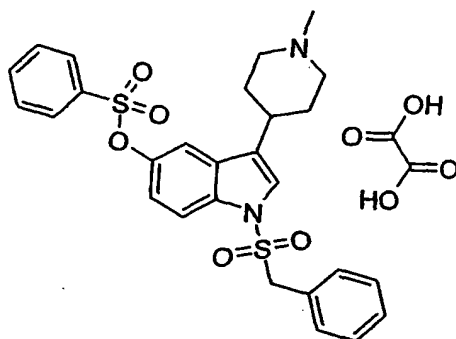
Example 14Benzenesulfonic acid 1-methylsulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (200 mg, 0.54 mmol), tetrahydrofuran (5 mL), potassium hydride (68 mg of a 35% dispersion in oil, 0.60 mmol), methanesulfonyl chloride (42 mL, 0.54 mmol) provided 37 mg (15%) of the free base of the desired compound as a colorless gum. This gum was converted to 38 mg (86%) of the title oxalate, isolated as an off-white solid: mp=95-99 °C. ¹H NMR (400 MHz, dmsO-d₆): 7.88-7.74 (m, 4H), 7.64 (t, 2H, J = 7.8 Hz), 7.41 (s, 1H), 7.33 (d, 1H, J = 2.8 Hz), 7.00 (dd, 1H, J = 9.0, 2.2 Hz). 3.46-3.36 (m, 2H), 3.43 (s, 3H), 3.00 (br t, 2H, J = 11.4 Hz), 2.91 (br t, 2H, J = 11.4 Hz), 2.74 (s, 3H), 2.00-1.90 (m 2H), 1.90-1.76 (m, 2H); MS (ES⁺): m/e 449.0 (M+1); MS (APCI): m/e 449.1 (M+1);

20 Calculated for C₂₁H₂₄N₂O₅S₂·C₂H₂O₄·0.5H₂O: calcd: C, 50.44; H, 4.97; N, 5.11; found: C, 50.47; H, 4.66; N, 4.97.

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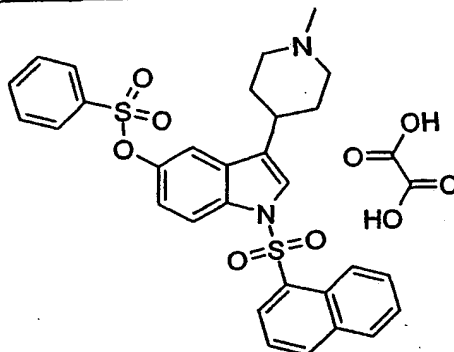
Example 15Benzenesulfonic acid 1-benzylsulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

- 5 By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (200 mg, 0.54 mmol), tetrahydrofuran (5 mL), potassium hydride (68 mg of a 35% dispersion in oil, 0.60 mmol), α -toluenesulfonyl chloride (225 mg, 1.08 mmol)
- 10 provided 30 mg (10%) of the free base of the desired compound as a tan gum. This gum was converted to 30 mg (85%) of the title oxalate, isolated as an off-white solid: mp=120-124 °C; ^1H NMR (400 MHz, $\text{dms}\text{-d}_6$): 7.86-7.77 (m, 3H), 7.65 (t, 2H, $J = 7.6$ Hz), 7.48 (d, 1H, $J = 9.2$ Hz), 7.28 (br s, 1H), 7.21 (d, 1H, $J = 7.6$ Hz), 7.09 (t, 2H, $J = 7.6$ Hz), 7.00 (br s, 1H), 6.88-6.80 (m, 3H), 4.95 (s, 2H), 3.50-3.30 (m, 2H), 3.10-2.90 (m, 2H), 2.90-2.75 (m, 1H), 2.74 (s, 3H), 1.90-1.78 (m 2H), 1.78-1.62 (m, 2H); MS (ES $^+$): m/e 525.0 (M+1);
- 15
- 20 Calculated (for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_5\text{S}_2 \cdot \text{C}_2\text{H}_2\text{O}_4$): C 56.67, H 4.92, N 4.56; found: C 56.71, H 4.88, N 4.35.

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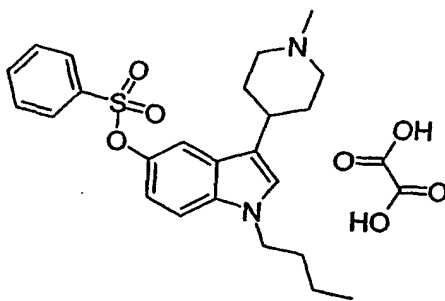
Example 16

Benzenesulfonic acid 1-(naphth-1-ylsulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



5 By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (200 mg, 0.54 mmol), tetrahydrofuran (5 mL), potassium hydride (68 mg of a 35% dispersion in oil, 10 0.60 mmol), naphth-1-ylsulfonyl chloride (245 mg, 1.08 mmol) provided 86 mg (28%) of the free base of the desired compound as a tan gum. This gum was converted to 92 mg (92%) of the title oxalate, isolated as a tan solid: mp=121-125 °C; ¹H NMR (400 MHz, dms_o-d₆): 8.59 (d, 1H, *J* = 8.0 Hz), 15 8.39 (d, 1H, *J* = 7.2 Hz), 8.30 (d, 1H, *J* = 7.6 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 7.99 (s, 1H), 7.82-7.52 (m, 9H), 7.27 (d, 1H, *J* = 2.0 Hz), 6.83 (dd, 1H, *J* = 9.0, 2.2 Hz), 3.48-3.30 (m, 2H), 3.07-2.80 (m, 3H), 2.75 (s, 3H), 1.95-1.70 (m, 4H); MS (APCI): *m/e* 561.1 (*M*+1); Calculated (for 20 C₃₀H₂₈N₂O₅S₂•C₂H₂O₄•0.7H₂O): C 57.94, H 4.77, N 4.22; found: C 57.98, H 4.45, N 4.01.

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Example 17Benzenesulfonic acid 1-butyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.50 g, 1.35 mmol), tetrahydrofuran (20 mL) potassium hydride (161 mg of a 35% dispersion in oil, 1.42 mmol) and 1-iodobutane (161 mL, 1.42 mmol) provided 305 mg (53%) of the free base of the desired product as a golden oil. The oil was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (64.3 mg, 0.71 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 315 mg (85%) of the title oxalate as an off-white solid: mp=193-198 °C; MS (APCI): m/e 427.2 (M+1); ¹H NMR (400 MHz, dms^o-d₆): 7.84-7.74 (m, 3H), 7.62 (t, 2H, J = 7.4 Hz), 7.37 (d, 1H, J = 8.8 Hz), 7.23 (s, 1H), 7.13 (br s, 1H), 6.68 (br d, 1H, J = 8.8), 4.04 (t, 2H, J = 7.0 Hz), 3.36 (br d, 2H, J = 11.6 Hz), 2.93 (br t, 2H, J = 11.8 Hz), 2.88-2.78 (m, 1H), 2.70 (s, 3H), 1.98-1.84 (m, 2H), 1.83-1.68 (m, 2H), 1.63 (quintuplet, 2H, J = 7.2 Hz), 1.18 (sextuplet, 2H, J = 7.2 Hz), 0.82 (t, 3H, J = 7.4 Hz); Calculated (for C₂₄H₃₀N₂O₃S•C₂H₂O₄): C 60.45, H 6.24, N 5.42; found: C 60.36, H 5.91, N 5.41.

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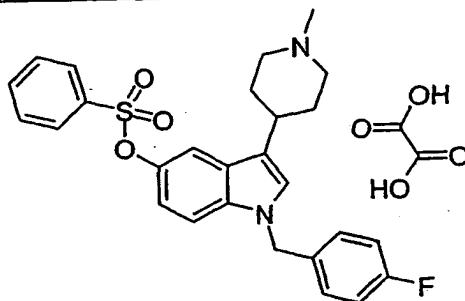
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Example 18

Benzenesulfonic acid 1-(4-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



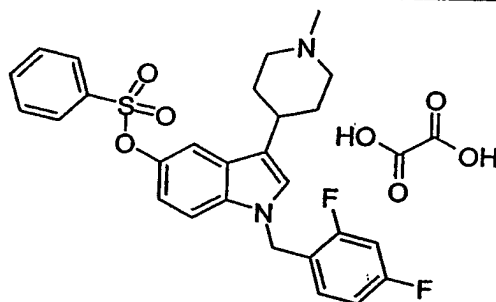
5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.40 g, 1.08 mmol) in tetrahydrofuran (20 mL) potassium hydride (129 mg of a 35% dispersion in oil, 1.11 mmol), 4-fluorobenzyl bromide (141 mL, 1.11 mmol) provided 340 mg (66%) of the free base of the desired product as a golden oil. The oil was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (63.9 mg, 0.71 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 371 mg (91%) of the title oxalate as a white solid: mp=181-184 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.84-7.73 (m, 3H), 7.66-7.58 (m, 2H), 7.41 (s, 1H), 7.39 (d, 1H, J = 8.8 Hz), 7.26-7.19 (m, 2H), 7.18 (d, 1H, J = 1.6 Hz), 7.14-7.06 (m, 2H), 6.66 (dd, 1H, J = 9.0, 2.2 Hz), 5.29 (s, 2H), 3.52-3.38 (m, 2H), 3.12-2.96 (m, 2H), 2.94-2.82 (m, 1H), 2.77 (s, 3H), 2.02-1.90 (m, 2H), 1.86-1.70 (m, 2H); MS (APCI): m/e 479.1 (M+1); Calculated (for C₂₇H₂₇FN₂O₃S•C₂H₂O₄•1.4H₂O): C 58.65, H 5.39, N 4.71; found: C 58.87, H 4.72, N 4.56.

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Example 19

Benzenesulfonic acid 1-(2,4-difluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.40 g, 1.08 mmol), tetrahydrofuran (20 mL), potassium hydride (129 mg of a 35% dispersion in oil, 1.11 mmol), 2,4-difluorobenzyl bromide (146 mL, 1.11 mmol) provided 357 mg (66%) of the free base of the desired product as a golden oil. The oil was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (64.7 mg, 0.71 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 390 mg (92%) of the title oxalate as a white solid: mp=141-144 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.86-7.72 (m, 3H), 7.61 (t, 2H, *J* = 7.8 Hz), 7.39 (d, 1H, *J* = 8.8 Hz), 7.29 (s, 1H), 7.22 (td, 1H, *J* = 9.6, 2.6 Hz), 7.17-7.08 (m, 2H), 6.98 (td, 1H, *J* = 8.4, 2.6 Hz), 6.72 (dd, 1H, *J* = 9.0, 2.2 Hz), 5.33 (s, 2H), 3.28 (br d, 2H, *J* = 11.6 Hz), 2.88-2.72 (m, 3H), 2.63 (s, 3H), 1.93-1.82 (m, 2H), 1.81-1.64 (m, 2H); MS (APCI): *m/e* 497.1 (*M*+1); Calculated (for C₂₇H₂₆F₂N₂O₃S•C₂H₂O₄): C 59.38, H 4.81, N 4.78; found: C 59.41, H 4.63, N 4.79.

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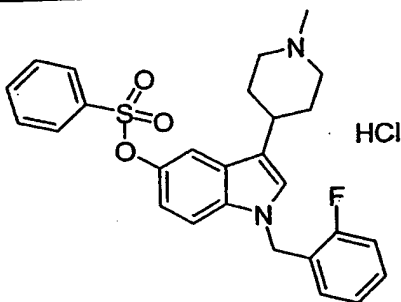
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Example 20

Benzenesulfonic acid 1-(2-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



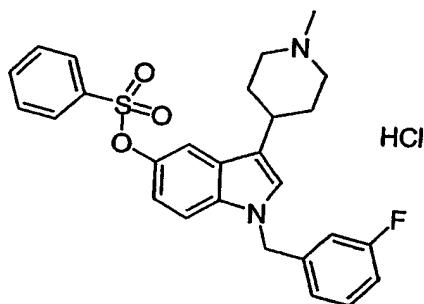
5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.40 g, 1.08 mmol), tetrahydrofuran (20 mL) potassium hydride (130 mg of a 35% dispersion in oil, 1.13 mmol) and 2-fluorobenzyl bromide (137 mL, 1.13 mmol) provided 63 mg (12%) of the free base of the desired product as a colorless oil. The oil was dissolved in methanol (10 mL) and treated with ammonium chloride (7.0 mg, 0.13 mmol, dissolved in 10 mL of methanol). The solvent was removed in vacuo, providing a solid residue, which was taken up in diethyl ether and sonicated for 5 minutes. Filtration and drying of the precipitate provided 61 mg (91%) of the title hydrochloride as a white solid: mp=222-224 °C; ¹H NMR (400 MHz, dms^o-d₆): 7.81 (d, 2H, J = 7.2 Hz), 7.76 (t, 1H, J = 7.4 Hz), 7.61 (t, 2H, J = 7.6 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.35-7.24 (m, 2H), 7.24-7.12 (m, 2H), 7.12-6.98 (m, 2H), 6.72 (br d, 1H, J = 7.6 Hz), 5.40 (s, 2H), 3.48-3.30 (m, 2H, overlapping with H₂O), 3.10-2.92 (m, 2H), 2.92-2.80 (m, 1H), 2.72 (s, 3H), 1.98-1.80 (m, 4H); MS (ES⁺): m/e 479.2 (M+1). Calculated (for C₂₇H₂₇FN₂O₃S•HCl•0.7H₂O): C 61.57, H 5.43, N 5.31; found: C 61.45, H 5.50, N 5.34.

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Example 21

Benzenesulfonic acid 1-(3-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

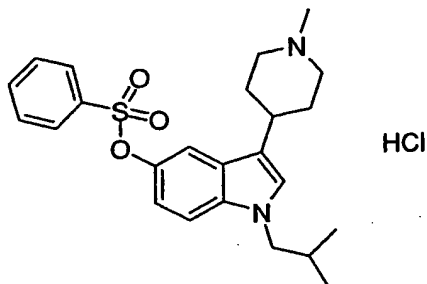


5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.40 g, 1.08 mmol), tetrahydrofuran (20 mL) potassium hydride (130 mg of a 35% dispersion in oil, 1.13 mmol) and 3-fluorobenzyl bromide (139 mL, 1.13 mmol) provided 309 mg (60%) of the free base of the desired product as yellow foam. The foam was further purified by preparative reverse-phase HPLC, which provided 293 mg (88%) of the title hydrochloride as an off-white solid: mp=103-105 °C; ¹H NMR (400 MHz, dms_o-d₆): 10.35 (br s, 1H), 7.81 (d, 2H, J = 7.2 Hz), 7.76 (t, 1H, J = 8.4 Hz), 7.61 (t, 2H, J = 8.0 Hz), 7.42 (s, 1H), 7.38 (d, 1H, J = 9.2 Hz), 7.35-7.25 (m, 1H), 7.23 (s, 1H), 7.10-6.93 (m, 3H), 6.68 (br d, 1H, J = 9.2 Hz), 5.33 (s, 2H), 3.43 (br d, 2H, J = 11.2 Hz), 3.10-2.95 (m, 2H), 2.95-2.80 (m, 1H), 2.74 (s, 3H), 2.00-1.80 (m, 4H); MS (ES⁺): m/e 479.1 (M+1); Calculated (for C₂₇H₂₇FN₂O₃S•HCl•0.5H₂O): C 62.00, H 5.39, N 5.35; found: C 61.14, H 5.33, N 5.28.

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Example 22Benzenesulfonic acid 1-isobutyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

5

By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.35 g, 0.9 mmol), tetrahydrofuran (20 mL) potassium hydride (113 mg of a 35% dispersion in oil, 1.0 mmol) and toluene-4-sulfonic acid isobutyl ester (1.08 g, 4.7 mmol) and isopropylmethyl tosylate (0.65 g, 0.28 mmol) provided 106 mg (26%) of the free base of the desired product as a colorless oil. The oil was dissolved in methanol (10 mL) and treated with ammonium chloride (13.3 mg, 0.25 mmol, dissolved in 10 mL methanol). The resulting solution was placed in an ultrasound bath for 15 minutes; then it was concentrated in vacuo to a residue, which was triturated with 9:1 diethyl ether-acetonitrile, upon which immediate formation of a precipitate was observed.

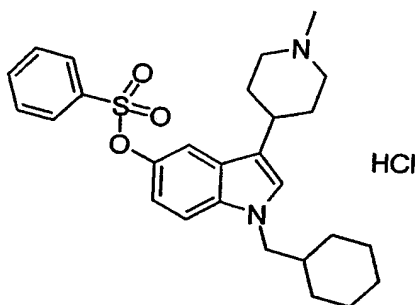
20 Sonication for 5 minutes, followed by filtration and drying of the solid afforded 83 mg (72%) of the title hydrochloride as a tan solid: mp=188-191 °C; ¹H NMR (400 MHz, dms_o-d₆): 10.84 (br s, 1H), 7.82 (d, 2H, J = 8.0 Hz), 7.76 (t, 1H, J = 7.4 Hz), 7.62 (t, 2H, J = 7.8 Hz), 7.38 (d, 1H, J = 9.2 Hz), 7.24-7.12 (m, 2H), 6.70 (d, 1H, J = 7.6 Hz), 3.86 (d, 2H, J = 7.2 Hz), 3.40 (br d, 2H, J = 11.6 Hz), 3.10-2.94 (m, 2H), 2.92-2.78 (m, 1H), 2.72 (s, 3H), 2.08-1.90 (m, 1H), 1.98-1.80 (m, 4H), 0.76 (d, 6H, J = 6.0 Hz); MS (APCI): m/e 427.2 (M+1); Calculated (for C₂₄H₃₀N₂O₃S•HCl): C 62.26, H 6.75, N 6.05; found: C 62.08, H 6.70, N 6.44.

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Example 23

Benzenesulfonic acid 1-cyclohexylmethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

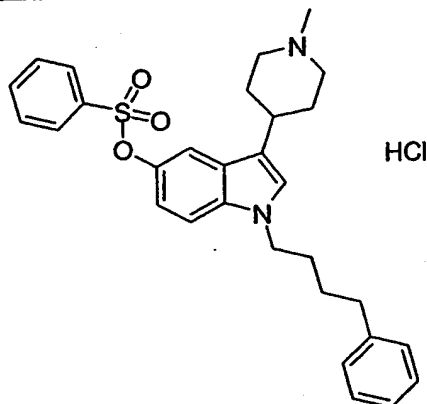


5 By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.30 g, 0.81 mmol) tetrahydrofuran (20 mL) potassium hydride (97 mg of a 35% dispersion in oil, 0.85 mmol) and cyclohexylmethyl bromide (226 mL, 1.62 mmol) and after 2 hours at 0°C provided 120 mg (31%) of the free base of the desired compound as a colorless oil. The oil was dissolved in methanol (5 mL) and treated with ammonium chloride (13.7 mg, 0.25 mmol, dissolved in 10 mL methanol). The resulting solution was placed in an ultrasound bath for 5 minutes before concentrating it in vacuo to a solid residue, which was triturated with diethyl ether and sonicated for 5 minutes. Filtration and drying of the precipitate afforded 111 mg (86%) of the title hydrochloride as a white solid: mp=98-101 °C; ¹H NMR (400 MHz, DMSO-d₆): 7.83 (d, 2H, J = 8.0 Hz), 7.76 (t, 1H, J = 7.4 Hz), 7.62 (t, 2H, J = 7.6 Hz), 7.37 (d, 1H, J = 8.8 Hz), 7.17 (d, 2H, J = 8.8 Hz), 6.71 (br d, 1H, J = 7.6 Hz), 3.88 (d, 2H, J = 6.8 Hz), 3.45-3.22 (m, 2H, overlapping with H₂O), 3.09-2.93 (m, 2H), 2.90-2.78 (m, 1H), 2.70 (s, 3H), 1.98-1.82 (m, 4H), 1.75-1.48 (m, 4H), 1.48-1.38 (m, 2H), 1.23-0.98 (m, 3H), 0.98-0.82 (m, 2H); MS (APCI): m/e 467.2 (M+1); Calculated (for C₂₇H₃₄N₂O₃S•HCl•1.6H₂O): C 61.08, H 7.06, N 5.27; found: C 61.26, H 6.77, N 5.25.

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Example 24

Benzenesulfonic acid 1-(4-phenylbutyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

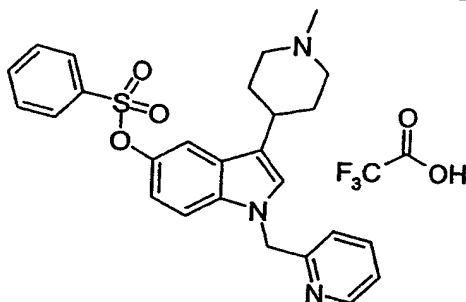


- 5 By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.30 g, 0.81 mmol) in tetrahydrofuran (20 mL) potassium hydride (97 mg of a 35% dispersion in oil, 0.85 mmol) and 1-chloro-4-phenylbutane (1.37 g, 8.1 mmol)
- 10 provided 32 mg (8%) of the free base of the title compound as a colorless film. The film was dissolved in methanol (10 mL) and treated with ammonium chloride (3.4 mg, 0.06 mmol, dissolved in 10 mL methanol). The resulting solution was placed in an ultrasound bath for 2 minutes and concentrated
- 15 in vacuo to a residue, which was triturated with diethyl ether. Sonication for 2 minutes, filtration, and drying of the precipitate afforded 27 mg (79%) of the title hydrochloride as a white solid: mp=158-161 °C; ¹H NMR (400 MHz, dmsO-d₆): 7.81 (d, 2H, J = 7.2 Hz), 7.56 (t, 1H, J = 7.2 Hz), 7.61 (t, 2H, J = 7.4 Hz), 7.36 (d, 1H, J = 8.8 Hz), 7.26-7.04 (m, 7H), 6.69 (d, 1H, J = 8.8 Hz), 4.07 (t, 2H, J = 6.8 Hz), 3.47-3.28 (m, 2H, overlapping with H₂O), 3.10-2.93 (m, 2H), 2.93-2.78 (m, 1H), 2.71 (s, 3H), 2.51 (t, 2H, J = 7.4 Hz), 1.98-1.80 (m, 4H), 1.74-1.60 (m, 2H), 1.53-1.40 (m, 2H); MS (ES⁺): m/e 503.0 (M+1); Calculated (for C₃₀H₃₄N₂O₃S•HCl•1.5H₂O): C 63.64, H 6.77, N 4.95; found: C 63.53, H 6.32, N 4.72.
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Example 25

Benzenesulfonic acid 1-(pyrid-2-ylmethyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester trifluoroacetate



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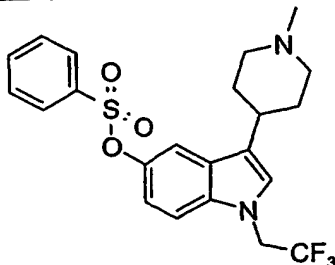
By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (0.20 g, 0.54 mmol) tetrahydrofuran (20 mL), potassium hydride (62 mg of a 35% dispersion in oil, 0.54 mmol) and 2-picolyl chloride free base (obtained by SCX purification of 443 mg, 2.7 mmol, of commercial 2-picolyl chloride hydrochloride) as a solution in tetrahydrofuran (3 mL) provided 28 mg (11%) of the free base of the title compound as a colorless film. The film was further purified by reverse-phase HPLC, which provided 25 mg (71%) of the corresponding trifluoroacetate salt as a white, filmy solid: MS (APCI): m/e 462.1 (M+1); ¹H NMR (400 MHz, CDCl₃): 8.54 (dd, 1H, J = 4.8, 1.2 Hz), 7.86-7.78 (m, 2H), 7.66-7.57 (m, 1H), 7.55-7.44 (m, 3H), 7.20-7.10 (m, 2H), 7.06 (d, 1H, J = 8.8 Hz), 6.97 (s, 1H), 6.73-6.64 (m, 2H), 5.32 (s, 2H), 2.97 (br d, 2H, J = 12.0 Hz), 2.66 (tt, 1H, J = 11.8, 3.6 Hz), 2.35 (s, 3H), 2.11 (td, 2H, J = 12.0, 1.2 Hz), 1.92 (br d, 2H, J = 13.2 Hz), 1.74 (qd, 2H, J = 12.4, 3.2 Hz).

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Example 26

Benzenesulfonic acid 1-(2,2,2-trifluoroethyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



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By a method similar to Example 1, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (435 mg, 1.17 mmol) dimethylformamide (10 mL), sodium hydride (47 mg of a 60% dispersion in oil, 1.17 mmol). 2,2,2-trifluoroethyl trifluoromethanesulfonate (273 mg, 1.17 mmol) provided 213 mg (40%) of the title compound as a white solid: mp=126-129 °C; ¹H NMR (400 MHz, CDCl₃): 7.86-7.78 (m, 2H), 7.67-7.60 (m, 1H), 7.48 (t, 2H, *J* = 7.6 Hz), 7.18-7.10 (m, 2H), 6.86 (s, 1H), 6.81 (dd, 1H, *J* = 9.0, 2.2 Hz), 4.52 (q, 2H, *J* = 8.8 Hz), 2.94 (br d, 2H, *J* = 11.2 Hz), 2.61 (tt, 1H, *J* = 12.0, 3.6 Hz), 2.33 (s, 3H), 2.08 (td, 2H, *J* = 11.6, 2.0 Hz), 1.88 (br d, 2H, *J* = 13.2 Hz), 1.70 (qd, 2H, *J* = 12.4, 3.4 Hz); MS (APCI): *m/e* 453.1 (*M*+1); Calculated (for C₂₂H₂₃F₃N₂O₃S) : C 58.40, H 5.12, N 6.19; found: C 58.00, H 5.05, N 6.02.

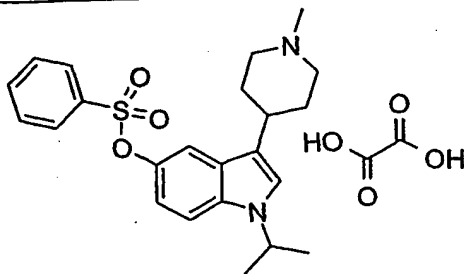
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Example 27

Benzenesulfonic acid 1-isopropyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

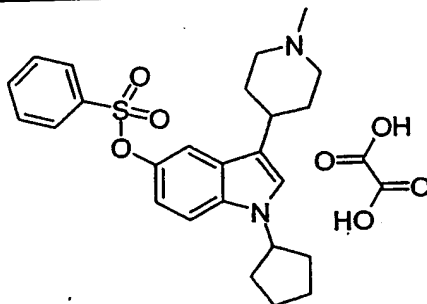


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To a solution of toluene-4-sulfonic acid isopropyl ester (1.45 g , 6.7 mmol) in dimethylformamide (20 mL) stirring at 0 °C, was added benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (250 mg, 0.67 mmol). The cold reaction mixture was then treated with sodium hydride in one portion (30 mg of a 60% dispersion in oil, 0.74 mmol), upon which the solution turned light yellow and then green. The mixture was diluted with methanol (20 mL) and directly applied to a 10 g SCX column. After thoroughly washing with methanol, the column was eluted with a 9:1 mixture of dichloromethane and 2 N ammonia in methanol. The eluent was concentrated *in vacuo* to a residue, which was further purified on silica gel. Elution with a 9:1 mixture of dichloromethane and methanol provided 171 mg (61%) of the free base of the title compound as an off-white foam. The foam was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (37.3 mg, 0.41 mmol, dissolved in 10 mL of ethyl acetate). A precipitate formed immediately, which was filtered and dried to provide 186 mg (89%) of the title oxalate as an off-white solid: mp=103-107 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.86-7.79 (m, 2H), 7.77 (br t, 1H, *J* = 7.6 Hz), 7.68-7.58 (m, 2H), 7.41 (d, 1H, *J* = 8.8 Hz), 7.33 (br s, 1H), 7.11 (br d, 1H, *J* = 2.0 Hz), 6.68 (dd, 1H, *J* = 9.2, 2.0 Hz), 4.63 (septuplet, 1H, *J* = 6.8 Hz), 3.36 (br d, 2H, *J* = 10.8 Hz), 3.02-2.88 (m, 2H), 2.88-2.77 (m, 1H), 2.71 (s, 3H), 1.98-1.87 (m, 2H), 1.87-1.70 (m, 2H), 1.36 (d, 6H, *J* = 6.4 Hz.); MS (ES⁺): *m/e* 413.1 (*M*+1); Calculated (for C₂₃H₂₆N₂O₃S•C₂H₂O₄•0.8H₂O) : C 58.08, H 6.16, N 5.42; found: C 58.14, H 5.86, N 5.56.

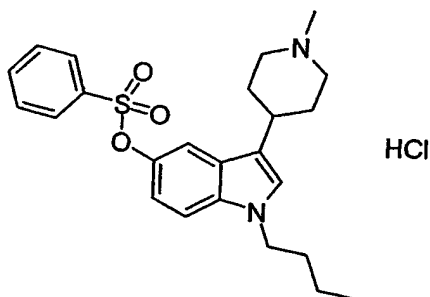
-67-

Example 28Benzenesulfonic acid 1-cyclopentyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5

By a method similar to Example 27, using toluene-4-sulfonic acid cyclopentyl ester (1.95 g, 8.1 mmol), dimethylformamide (20 mL), benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 34 or 45, (250 mg, 0.67 mmol), sodium hydride (36 mg of a 60% dispersion in oil, 0.89 mmol) provided 158 mg (44%) of the free base of the desired compound as a colorless gum. The gum was dissolved in ethyl acetate (10 mL) and treated with oxalic acid (32.4 mg, 0.36 mmol, dissolved in 10 mL ethyl acetate), upon which a precipitate formed immediately. Filtration and drying of the precipitate provided 162 mg (85%) of the title oxalate as an off-white solid: mp=202-205 °C; ¹H NMR (400 MHz, dms_o-d₆): 7.84-7.74 (m, 3H), 7.62 (t, 2H, *J* = 7.6 Hz), 7.41 (d, 1H, *J* = 9.2 Hz), 7.30 (s, 1H), 7.13 (d, 1H, *J* = 2.4 Hz), 6.68 (dd, 1H, *J* = 9.0, 2.2 Hz), 4.80-4.70 (m, 1H), 3.38 (br d, 2H, *J* = 11.2 Hz), 2.98 (br t, 2H, *J* = 11.2 Hz), 2.90-2.78 (m, 1H), 2.73 (s, 3H), 2.12-2.00 (m, 2H), 1.98-1.86 (m, 2H), 1.86-1.68 (m, 6H), 1.68-1.56 (m, 2H); MS (ES⁺): *m/e* 439.1 (M+1); Calculated (for C₂₅H₃₀N₂O₃S•C₂H₂O₄): C 61.35, H 6.10, N 5.30; found: C 61.30, H 6.16, N 5.02.

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Example 29Benzenesulfonic acid 1-butyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

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The oxalate salt of benzenesulfonic acid 1-butyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 17, (0.25 g) was dissolved in methanol (25mL) and directly applied to a 2 g SCX column. After thoroughly washing with methanol, the column was eluted with a 2:1 mixture of dichloromethane and 2 N ammonia in methanol. The eluent was concentrated *in vacuo* to provide 204 mg of the corresponding free base as a golden oil. The oil was dissolved in methanol (10 mL) and treated with ammonium chloride (25.6 mg, 0.47 mmol, dissolved in 10 mL methanol). The resulting solution was concentrated *in vacuo*, and the residue triturated with a minimal amount of diethyl ether-acetonitrile. Filtration and drying of the precipitate provided 183 mg (82%) of the title hydrochloride as a white solid: mp=169-172 C; MS (APCI): m/e 427.2 (M+1); Calculated (for C₂₄H₃₀N₂O₃S•HCl•0.2H₂O): C 61.77, H 6.78, N 6.00; found: C 61.72, H 6.52, N 5.92.

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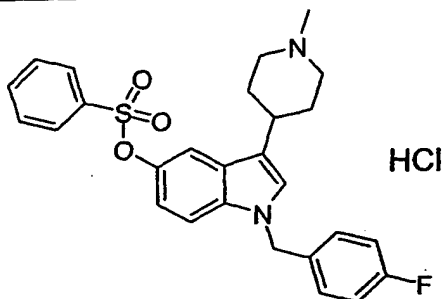
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Example 30

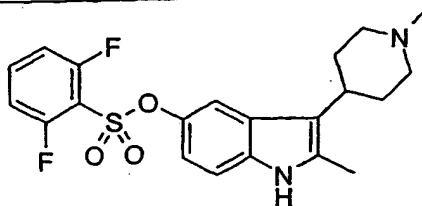
Benzenesulfonic acid 1-(4-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



5 The oxalate salt of benzenesulfonic acid 1-(4-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, from example 18, (0.30 g) was dissolved in methanol (25 mL) and directly applied to a 2 g SCX column. After thoroughly washing with
10 methanol, the column was eluted with a 2:1 mixture of dichloromethane and 2 N ammonia in methanol. The eluent was concentrated in vacuo to provide 244 mg of the corresponding free base as a golden oil. The oil was dissolved in
15 methanol (10 mL) and treated with ammonium chloride (27.2 mg, 0.51 mmol, dissolved in 10 mL methanol). The resulting solution was concentrated in vacuo, and the residue triturated with a minimal amount of diethyl ether. Filtration and drying of the precipitate provided 226 mg
20 (86%) of the title hydrochloride as a white solid: mp=169-172 °C; MS (APCI): m/e 479.2 (M+1); Calculated (for C₂₇H₂₇FN₂O₃S•HCl•0.8H₂O): C 61.25, H 5.63, N 5.29; found: C 61.20, H 5.42, N 5.68.

Example 31

25 2,6-Difluorobenzenesulfonic acid 2-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

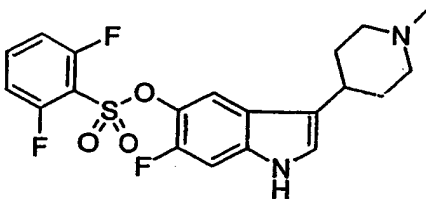


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A solution of 2-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (4.05 mmol, 0.989 g) in THF (12 mL) and 1M sodium hydroxide (4.09 mL) was treated with 2,6-difluorobenzenesulfonyl chloride (4.46 mmol, 0.948g). After stirring one hour at room temperature the reaction was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The organic phases were combined, concentrated in vacuo to afford foam. The free amine was converted to the hydrochloride salt. Acetyl chloride (approximately 1.2 eq) was added to a cooled solution of ethanol (0 °C). After stirring approximately five minutes, this solution was added to a solution of the free amine in ethanol. The biphasic solution was concentrated in vacuo to foam. The foam was dissolved in acetone, crystals formed, collected by filtration to afford 1.12 g (60%) of the title compound: mp =138 °C (decomposes); mass spectrum (ion spray): m/z = 420(M-1); Calculated for C₂₁H₂₂F₂N₂O₃S-HCl-0.2H₂O-0.6C₃H₆O: C, 55.28; H, 5.49; N, 5.66. Found: C, 55.42; H, 5.46; N, 5.30

Example 32

2,6-Difluorobenzenesulfonic acid 6-fluoro-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



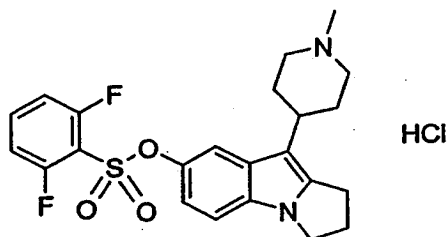
By a method similar to Example 31, using 0.2N sodium hydroxide (2.4 mmol, 12.2 mL), 2,6-difluorobenzenesulfonyl chloride (2.9 mmol, 0.625 g), 6-fluoro-3-(1-methylpiperidin-4-yl)-1H-indole-5-ol (2.4 mmol, 0.608 g) in THF (7.7 mL). The crude isolated product was subjected to normal phase silica gel radial chromatography, 4mm plate eluting with 9:1 methylene chloride:2M ammonia in methanol at 10 mL/minute. Fractions containing product combined, concentrated in vacuo to a white solid. The title compound was crystallized from methylene chloride to afford 0.282 g (27%) of the title

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compound: mp=202 °C; Mass spectrum (ion spray): m/z
=425 (M+1); ¹H NMR (DMSO-d₆): 11.10 (s, 1H), 7.91 (m, 1H), 7.40
(m, 2H), 7.26-7.16 (m, 3H), 2.78 (m, 2H), 2.52 (m, 1H), 2.20
(s, 3H), 1.96 (m, 2H), 1.69 (m, 2H), 1.51 (m, 2H);
5 Calculated for C₂₀H₁₉F₃N₂O₃S: C, 56.12; H, 4.57; N, 6.54.
Found: C, 56.13; H, 4.56; N, 6.48.

Example 33

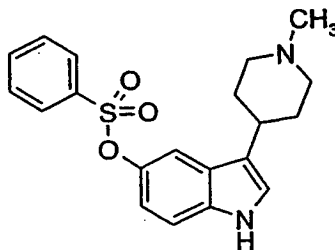
10 2,6-Difluorobenzenesulfonic acid 9-(1-methylpiperidin-4-yl)-
2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-yl ester hydrochloride



By a method similar to Example 31, using 9-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-6-ol (270 mg, 1.0 mmol) in NaOH (6.5 mL, 1.3 mmol, 0.2 N), THF
15 (3.0 mL). and 2,6-difluorobenzenesulfonyl chloride gave a crude residue that was purified by PCTLC (silica gel GF rotor; 95:5 CHCl₃:2M NH₃ in MeOH) and the hydrochloride formed in EtOAc affording 388 mg (81%) of the title compound as a white powder: mp=149°C (transition) and 229°C; MS
20 (ES⁺): m/e 447.1 (M+1); Calculated for C₂₃H₂₄F₂N₂O₃SHCl: Calcd: C, 57.20; H, 5.22; N, 5.80. Found: C, 56.90; H, 5.07; N, 5.74.

Example 34

25 Benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

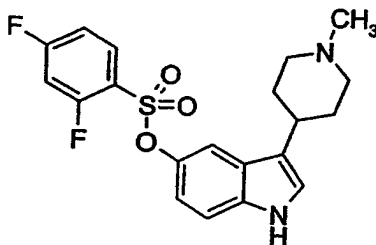


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By a method similar to Example 31, using benzenesulfonyl chloride (280 μ L, 2.2 mmol), 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (418 mg, 1.8 mmol) in 0.2 N sodium hydroxide (10 mL, 2.0 mmol) and THF (6mL) gave 650 mg of an off white solid. The crude product was recrystallized from ethyl acetate to give 505 mg (75%) of tan needles: mp= 192-194 $^{\circ}$ C; MS(m/e): 370 (M^{+}); Calculated for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56. Found: C, 64.92; H, 6.19; N, 7.67.

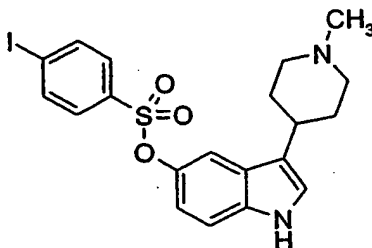
Example 35

2,4-Difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



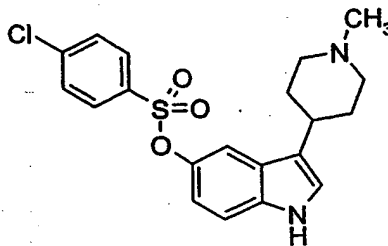
By a method similar to Example 31, using 2,4-difluorobenzenesulfonyl chloride (463 mg, 2.2 mmol) was added to a solution of 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (418 mg, 1.8 mmol) in 0.2 N sodium hydroxide (10 mL, 2.0 mmol) and THF (5 mL) gave 735 mg of product. The crude product was recrystallized from ethyl acetate/hexanes to give 680 mg (92%) of white crystals: mp=163-164 $^{\circ}$ C; MS(m/e): 406 (M^{+}); Calculated for $C_{20}H_{20}F_2N_2O_3S$: C, 59.10; H, 4.96; N, 6.89. Found: C, 58.86; H, 4.94; N, 6.95.

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Example 364-Iodobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

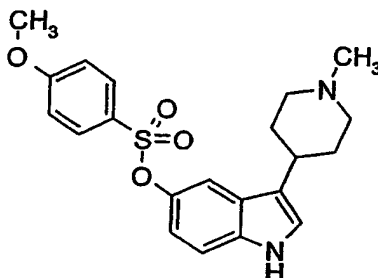
5 By a method similar to Example 31, using 4-Iodobenzenesulfonyl chloride (347 mg, 1.15 mmol) in THF (4 mL), 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (220 mg, 0.96 mmol) in 0.2 N sodium hydroxide (5.2 mL, 1.05 mmol) and
10 THF (4 mL) gave 470 mg of an off white solid. The crude product was recrystallized from ethyl acetate/hexanes to give 404 mg (85%) of tan crystals: mp=174-176 °C; MS(m/e): 495 (M-1); Calculated for C₂₀H₂₁IN₂O₃S: Calcd: C, 48.40; H, 4.26; N, 5.64. Found: C, 48.74; H, 4.20; N, 5.59.

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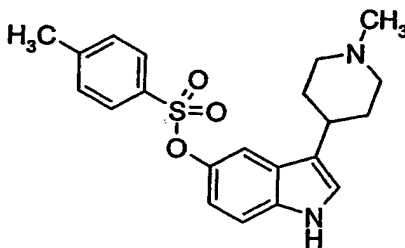
Example 374-Chlorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

20 By a method similar to Example 31, using 4-chlorobenzenesulfonyl chloride (242 mg, 1.15 mmol) and 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (220 mg, 0.96 mmol), 0.2 N sodium hydroxide (5.5 mL, 1.1 mmol) gave 380 mg of a white solid. The crude product was recrystallized from
25 ethyl acetate/hexanes to give 300 mg (78%) of the title compound as an off white powder: mp=182-183.5 °C; MS(m/e): 404 (M⁺); Calculated for C₂₀H₂₁ClN₂O₃S: C, 59.33; H, 5.23; N, 6.92. Found: C, 59.24; H, 5.22; N, 6.90.

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Example 384-Methoxybenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

By a method similar to Example 31, using 4-methoxybenzenesulfonyl chloride (248 mg, 1.2 mmol) and 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (230 mg, 1.0 mmol), 0.2 N sodium hydroxide (5.5 mL, 1.1 mmol) gave 225 mg of crude product. The crude product was recrystallized from ethyl acetate to give 195 mg (49%) of the title compound as a white powder: mp=186-187 °C; MS(m/e): 400 (M⁺); Calculated for C₂₁H₂₄N₂O₄S: Calcd: C, 62.98; H, 6.04; N, 6.99. Found: C, 63.10; H, 6.18; N, 7.04.

Example 394-Methylphenylsulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

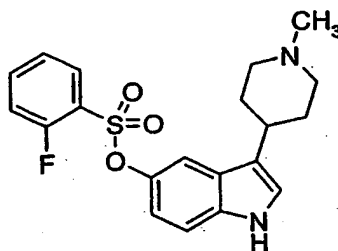
By a method similar to Example 31, using 4-methylbenzenesulfonyl chloride (228 mg, 1.2 mmol) and 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (230 mg, 1.0 mmol), 0.2 N sodium hydroxide (5.5 mL, 1.1 mmol) gave 400 mg of crude product. The crude product was recrystallized from ethyl acetate to give 305 mg (79%) of a white powder: mp=186-187 °C. MS(m/e): 384 (M⁺); Calculated for C₂₁H₂₄N₂O₃S:

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Calcd: C, 65.60; H, 6.29; N, 7.29. Found: C, 65.50; H, 6.35; N, 7.23.

Example 40

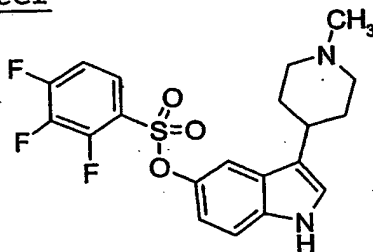
5 2-Fluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



By a method similar to Example 31, using 2-fluorobenzenesulfonyl chloride (234 mg, 1.2 mmol) added dropwise to a solution of 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (231 mg, 1.0 mmol) in 0.2 N sodium hydroxide (5.5 mL, 1.1 mmol) and THF (5 mL) gave 448 mg of the title compound as a crystalline solid. The product was recrystallized from ethyl acetate/hexanes to give 320 mg (82%) of the title compound an off white powder: mp=180-182 °C; MS(m/e): 389 (M+1); Calculated for C₂₀H₂₁FN₂O₃S: Calcd: C, 61.84; H, 5.45; N, 7.21. Found: C, 61.83; H, 5.57; N, 7.26.

Example 41

20 2,3,4-Trifluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



By a method similar to Example 31, using 2,3,4-trifluorobenzenesulfonyl chloride (280 mg, 1.2 mmol) and 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (231 mg, 1.0 mmol) and 0.2 N sodium hydroxide (5.5 mL, 1.1 mmol) gave 449 mg of a purple foam. The crude product was purified by

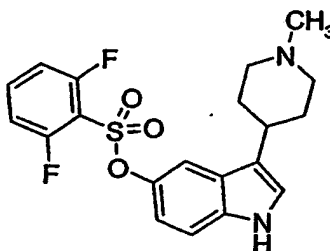
-76-

radial chromatography (silica gel, 2000 micron rotor, 100/10 methylene chloride/methanol then 100/10/0.5 methylene chloride/methanol/ammonium hydroxide) to give 418 mg (98%) of homogeneous product. The product was crystallized from ethyl acetate/hexanes to give 280 mg of the title compound as a white powder: mp=160-162 °C; MS(m/e): 424 (M⁺); Calculated for C₂₀H₁₉F₃N₂O₃S: C, 56.60; H, 4.51; N, 6.60. Found: C, 56.53; H, 4.78; N, 6.51.

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Example 42

2,6-Difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

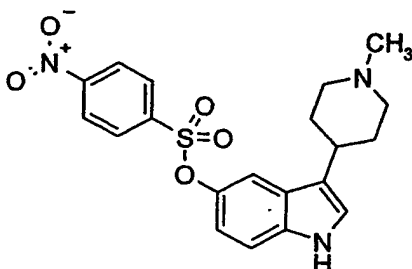


By a method similar to Example 31, using 2,6-difluorobenzenesulfonyl chloride (256 mg, 1.2 mmol) and 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (231 mg, 1.0 mmol), and 0.2 N sodium hydroxide (5.5 mL, 1.1 mmol) gave 400 mg (98%) of the title compound as an off white powder were obtained. The product was recrystallized from ethyl acetate/methanol/hexanes: mp=214-215 °C; MS(m/e): 407 (M+1); Calculated for C₂₀H₂₀F₂N₂O₃S: C, 59.10; H, 4.96; N, 6.89. Found: C, 59.07; H, 5.16; N, 6.73.

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Example 43

4-Nitrobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



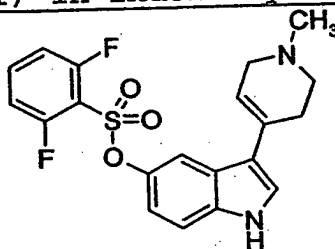
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By a method similar to Example 31, using 4-nitrobenzenesulfonyl chloride (997 mg, 4.05 mmol) was added to a mixture of 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (777 mg, 3.4 mmol) in 0.2 N sodium hydroxide (18.6 mL, 3.7 mmol) and THF (20 mL) gave 1.4 g of an orange foam. The product was crystallized from ethyl acetate/hexanes to give 485 mg (35%) of an orange powder. The mother liquors were purified by flash chromatography (silica gel, 5%, 7% 2M ammonia in methanol/ methylene chloride) to give 800 mg (57%) of the title compound as yellow foam: Total yield was 92%; mp=171-172 °C; MS(m/e): 416 (M+1), 414 (M-1); Calculated for C₂₀H₂₁N₃O₅S: C, 57.82; H, 5.09; N, 10.11. Found: C, 57.35; H, 4.96; N, 9.88.

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Example 44

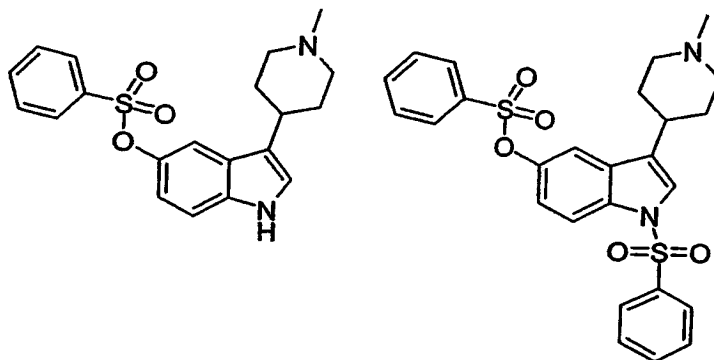
2,6-Difluorobenzenesulfonic acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester



By a method similar to Example 31, using a solution of 2,6-difluorobenzenesulfonyl chloride (380 mg, 1.79 mmol) in THF (5 mL) was added to a mixture of 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5-hydroxy-1H-indole (340 mg, 1.49 mmol) in 0.2 N sodium hydroxide (8.2 mL, 1.64 mmol) and THF (5 mL) gave 170 mg (28%) of homogeneous product as a tan solid. The product was crystallized from ethyl acetate to give 96 mg (16%) of the title compound as a yellow powder: mp 183 °C dec; MS(m/e): 405 (M+1), 403 (M-1); Calculated for C₂₀H₁₈F₂N₂O₃S: C, 59.40; H, 4.49; N, 6.93. Found: C, 59.22; H, 4.24; N, 6.65.

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Example 45Benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-
yl ester and5 Benzenesulfonic acid 1-benzenesulfonyl-3-(1-
methylpiperidine-4-yl)-1H-indol-5-yl ester

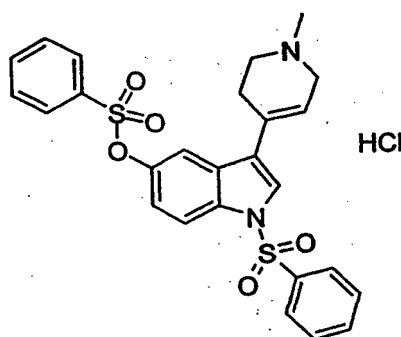
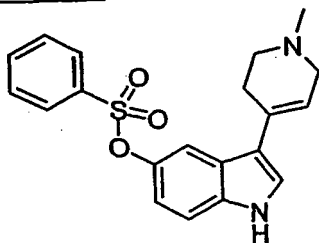
To a solution of 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (4.75 g, 20.6 mmol) in dimethylformamide (25 mL), stirring at 0 °C under nitrogen, was added sodium hydride in one portion (0.83 g of a 60% dispersion in oil, 20.6 mmol). The green solution turned brown; after stirring for 30 minutes at 0°C benzenesulfonyl chloride (2.63 mL, 20.6 mmol) was added in one portion, then the reaction mixture was allowed to stir until the reaction was complete. The solution was poured into water (125 mL), then extracted with ethyl acetate (4 x 125 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo to a residue which was further purified on silica gel. Elution with a 9:1 mixture of dichloromethane and 2 N ammonia in methanol provided 5.40 g (70%) of benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester as a tan solid: mp=189-194 °C; ¹H NMR (400 MHz, dms_o-d₆): 10.97 (br s, 1H), 7.85-7.72 (m, 3H), 7.65-7.54 (m, 2H), 7.24 (d, 1H, J = 8.8 Hz), 7.11 (d, 1H, J = 2.0 Hz), 6.88 (d, 1H, J = 1.2 Hz), 6.69 (dd, 1H, J = 8.8, 1.6 Hz), 2.77 (br d, 2H, J = 11.2 Hz), 2.52-2.40 (m, 1H), 2.16 (s, 3H), 1.91 (br t, 2H, J = 11.2 Hz), 1.67 (br d, 2H, J = 12.0 Hz), 1.58-1.44 (m, 2H); MS(ES⁺): m/e 371.0 (M+1).

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Benzenesulfonic acid 1-benzenesulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester was also obtained as a side product. Chromatography provided 290 mg (3%) of the aforementioned compound as a gold-colored oil. A solution of the oil in methanol (10 mL) was treated with ammonium chloride (30.3 mg, 0.56 mmol, dissolved in 10 mL of methanol). Concentration in vacuo, followed by trituration in a minimal amount of diethyl ether, filtration, and drying of the resulting precipitate afforded 272 mg (87%) of benzenesulfonic acid 1-benzenesulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester as a tan solid: mp=123-127 °C; MS (ES+): m/e 511.0 (M+1); ¹H-NMR (400 MHz, dms_o-d₆): 7.98-7.92 (m, 2H), 7.90-7.84 (m, 1H), 7.82-7.74 (m, 3H), 7.70-7.64 (m, 1H), 7.64-7.52 (m, 5H), 7.04-6.98 (m, 2H), 2.77 (br d, 2H, J = 10.8 Hz), 2.52-2.40 (m, 1H), 2.17 (s, 3H), 1.91 (br t, 2H, J = 10.8 Hz), 1.68-1.58 (m, 2H), 1.56-1.42 (m, 2H); Calculated (for C₂₆H₂₆N₂O₅S₂•HCl•1.5H₂O) : C 54.39, H 5.26, N 4.88, Cl 6.17; found: C 54.21, H 4.93; N 5.06; Cl 6.38.

Example 46

Benzenesulfonic acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester and Benzenesulfonic acid 1-(benzenesulfonyl) acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester hydrochloride



By a method similar to Example 45, using 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5-hydroxy-1H-indole (1.25 g, 5.47 mmol) in dimethylformamide (20 mL), sodium hydride (0.22 g of a 60% dispersion in oil, 5.47 mmol), and

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benzenesulfonyl chloride (699 μ L, 5.47 mmol) provided 700 mg (35%) of Benzenesulfonic acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester as a tan solid: mp=186-190 $^{\circ}$ C; MS (APCI): m/e 369.3 (M+1); 1 H NMR (400 MHz, dms o -d $_6$): 11.32 (br s, 1H), 7.90-7.80 (m, 2H), 7.77 (t, 1H, J = 7.2 Hz), 7.62 (t, 2H, J = 7.6 Hz), 7.41 (d, 1H, J = 2.4 Hz), 7.30 (d, 1H, J = 8.8 Hz), 7.13 (d, 1H, J = 2.4 Hz), 6.74 (dd, 1H, J = 8.8, 2.4 Hz), 5.60 (br s, 1H), 2.97-2.91 (m, 2H), 2.49 (br t, 2H, J = 5.6 Hz), 2.42-2.36 (m, 2H), 2.24 (s, 3H).

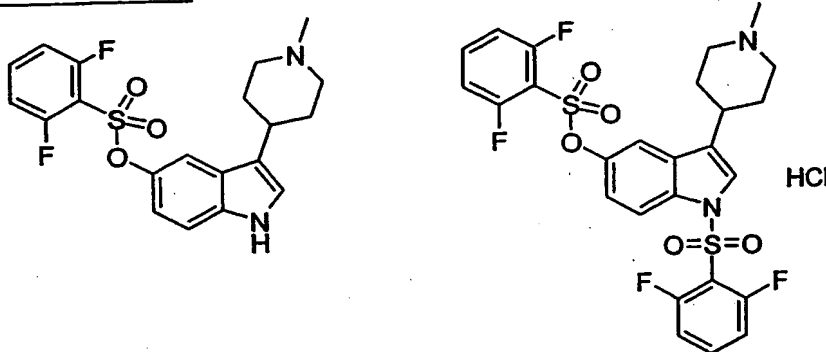
Benzenesulfonic acid 1-benzenesulfonyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester hydrochloride 450 mg (16%) was isolated by chromatography as a gold colored oil which was dissolved in methanol (10 mL) and treated with ammonium chloride (65.3 mg, 1.22 mmol, added as a solution in 10 mL of methanol). The solution was concentrated in vacuo, and the residue was triturated in a minimal amount of diethyl ether. Separation of the supernatant followed and drying of the precipitate afforded 270 mg (56%) of benzenesulfonic acid 1-benzenesulfonyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester hydrochloride as a white solid: mp=257-260 $^{\circ}$ C; 1 H NMR (400 MHz, dms o -d $_6$): 10.62 (br s, 1H), 8.06 (s, 1H), 8.02-7.99 (m, 2H), 7.92 (d, 1H, J = 9.2 Hz), 7.83-7.79 (m, 3H), 7.72-7.66 (m, 1H), 7.65-7.56 (m, 4H), 7.38 (d, 1H, J = 2.0 Hz), 6.97 (dd, 1H, J = 8.8, 2.4 Hz), 5.93 (br s, 1H), 3.97-3.85 (m, 1H), 3.76-3.62 (m, 1H), 3.60-3.48 (m, 1H), 3.28-3.15 (m, 1H), 2.88-2.72 (m, 2H), 2.82 (s, 3H); IR (KBr): 3431, 3145, 2671, 2539, 1583, 1577, 1455, 1448, 1351, 1195, 1175, 1166 cm^{-1} ; MS (APCI): m/e 509.4 (M+1); Calculated (for $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5\text{S}_2 \cdot 0.9\text{HCl} \cdot 0.1\text{H}_2\text{O}$) : C 57.49, H 4.66, N 5.16; found: C 57.85, H 4.73, N 5.30.

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Example 47

2,6-Difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester and

- 5 2,6-Difluorobenzenesulfonic acid 1-(2,6-difluoro-
benzenesulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl
ester hydrochloride



- By a method similar to Example 45, using 3-(1-methyl-
 10 pyridin-4-yl)-5-hydroxy-1H-indole (1.50 g, 6.5 mmol) in
 dimethylformamide (40 mL), sodium hydride (0.29 g of a 60%
 dispersion in oil, 7.2 mmol), 2,6-difluorobenzenesulfonyl
 chloride (1.52 g, 7.2 mmol) provided 1.35 g (51%) of 2,6-
 difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-
 15 indol-5-yl ester as an off-white solid: mp 235-238 °C;
 MS(ES⁺): m/e 407.0 (M+1); ¹H NMR (400 MHz, dms_o-d₆): 11.04
 (br s, 1H), 7.92-7.82 (m, 1H), 7.42-7.33 (m, 2H), 7.29 (d,
 1H, J = 8.8 Hz), 7.15 (d, 1H, J = 2.0 Hz), 7.06 (d, 1H, J =
 2.0 Hz), 6.79 (dd, 1H, J = 8.8, 1.8 Hz), 2.78 (br d, 2H, J =
 20 11.2 Hz), 2.56-2.46 (m, 1H), 2.16 (s, 3H), 1.93 (br t, 2H, J
 = 11.8 Hz), 1.74-1.64 (m, 2H), 1.60-1.46 (m, 2H).

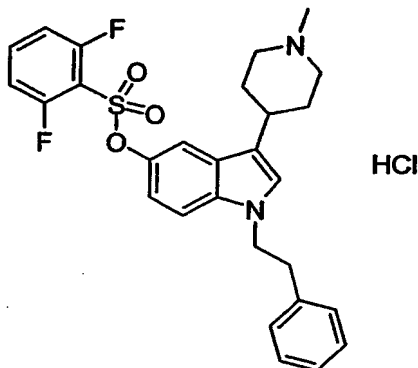
- 2,6-Difluorobenzenesulfonic acid 1-(2,6-difluoro-
 benzenesulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl
 ester was also obtained. Chromatography provided 236 mg (6%)
 25 of the aforementioned compound as a yellow solid. The free
 base was dissolved in methanol (10 mL) and treated with
 ammonium chloride (21.6 mg, 0.41 mmol, dissolved in 10 mL of
 methanol). The resulting solution was concentrated in
 vacuo, and the residue was triturated with a minimal amount

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- of diethyl ether. Filtration and drying of the precipitate provided 219 mg (87%) of 2,6-difluorobenzenesulfonic acid 1-(2,6-difluoro-benzenesulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester as an off-white solid: mp 95-98 °C; MS (ES+): m/e 583.0 (M+1); ¹H NMR (400 MHz, dms_o-d₆): 7.96-7.84 (m, 1H), 7.84-7.74 (m, 1H), 7.71 (d, 1H, J = 9.2 Hz), 7.62-7.52 (m, 2H), 7.42-7.28 (m, 4H), 7.10 (br d, 1H, J = 8.8 Hz), 3.40-3.22 (br m, 2H, overlapping with H₂O), 3.04-2.82 (br m, 3H), 2.68 (br s, 3H), 2.00-1.78 (br m, 4H);
- 10 Calculated (for C₂₆H₂₂F₄N₂O₅S₂•HCl•0.6H₂O): C 49.58, H 3.87, N 4.44, Cl 5.62; found: C 49.58, H 3.76, N 4.51, Cl 5.48.

Example 48

- 15 2,6-Difluorobenzenesulfonic acid 1-phenethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



- To a solution of 1-phenethyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (175 mg, 0.52 mmol) and 2,6-difluorobenzenesulfonyl chloride (133 mg, 0.58 mmol) in tetrahydrofuran (20 mL), stirring at room temperature, was added 2,6-lutidine dropwise (134 mL, 1.16 mmol). The reaction mixture was stirred for 72 hours at room temperature, before diluting it with methanol (15 mL) and applying it directly to a 5 g SCX column. After thoroughly washing with methanol, the column was eluted with a 9:1 mixture of dichloromethane and 2 N ammonia in methanol. The eluent was concentrated in vacuo to a residue, which was purified on silica gel. Elution with a 9:1 mixture of dichloromethane and methanol provided 191 mg (64%) of the

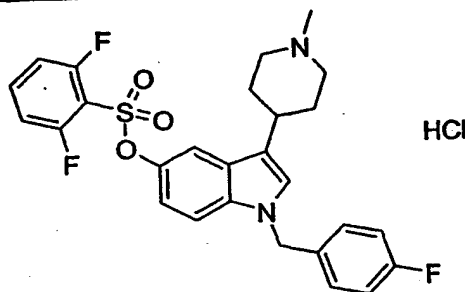
-83-

free base of the desired compound as a tan gum. The gum was further purified by preparative reverse-phase HPLC, which provided 156 mg (44%) of the title hydrochloride as an off-white solid: mp=209-212 °C; ¹H NMR (400 MHz, dmsO-d₆): 10.55

- 5 (br s, 1H), 7.95-7.82 (m, 1H), 7.48-7.34 (m, 3H), 7.30 (s, 1H), 7.25-7.08 (m, 6H), 6.76 (br d, 1H, *J* = 8.4 Hz), 4.29 (t, 2H, *J* = 7.4 Hz), 3.41 (br d, 2H, *J* = 12.4 Hz), 3.10-2.97 (m, 2H), 2.96 (t, 2H, *J* = 7.0 Hz), 2.94-2.82 (m, 2H), 2.72 (s, 3H), 1.96-1.75 (m, 4H); MS (APCI): *m/e* 511.2 (*M*+1);
- 10 Calculated (for C₂₈H₂₈F₂N₂O₃S•HCl•0.6H₂O) : C 60.39, H 5.28, N 5.03; found: C 60.43, H 5.41, N 5.14.

Example 49

- 15 2,6-Difluorobenzenesulfonic acid 1-(4-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

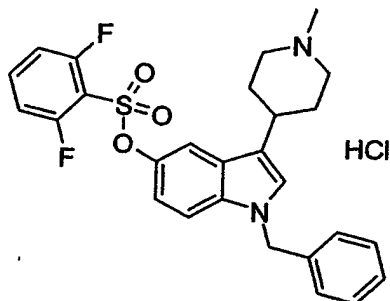


- By a method similar to Example 48, using 1-(4-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (325 mg, 0.96 mmol), 2,6-difluorobenzenesulfonyl chloride (306 mg, 1.44 mmol) in tetrahydrofuran (20 mL), 2,6-lutidine dropwise (335 mL, 2.88 mmol) gave 323 mg (65%) which provided 303 mg (93%) of the corresponding hydrochloride salt as a white solid: mp=114-118 °C; ¹H NMR (400 MHz, dmsO-d₆): 10.43 (br s, 1H), 7.93-7.82 (m, 1H), 7.50-7.30 (m,
- 20 5H), 7.28-7.18 (m, 2H), 7.15-7.03 (m, 2H), 6.78 (dd, 1H, *J* = 8.8, 1.6 Hz), 5.31 (s, 2H), 3.42 (br d, 2H, *J* = 11.2 Hz), 3.14-2.98 (m, 2H), 2.98-2.87 (m, 1H), 2.73 (s, 3H), 2.03-1.80 (m, 4H); MS (ES⁺): *m/e* 515.1 (*M*+1); Calculated (for C₂₇H₂₅F₃N₂O₃S•HCl•1.5H₂O): C 56.20, H 4.89, N 4.85; found: C
- 25 56.11, H 4.53, N 4.64.
- 30

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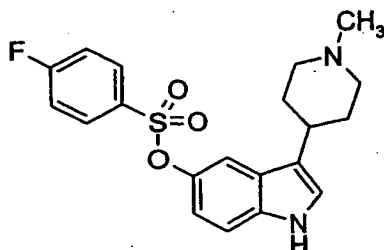
Example 50

2,6-Difluorobenzenesulfonic acid 1-benzyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



5 By a method similar to Example 48, using 1-benzyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (320 mg, 1.0 mmol), 2,6-difluorobenzenesulfonyl chloride (234 mg, 1.1 mmol) in tetrahydrofuran (20 mL), 2,6-lutidine (255 μ L, 2.2 mmol) provided 382 mg (77%) of the free base of the desired
10 compound as a colorless oil. A portion of this oil (182 mg) was dissolved in methanol (10 mL) and treated with ammonium chloride (19.6 mg, 0.37 mmol, dissolved in 10 mL methanol). The resulting solution was placed in an ultrasound bath for 5 minutes before removing the solvent *in vacuo*. The
15 resulting residue was triturated with diethyl ether. Filtration and drying of the precipitate afforded 160 mg (82%) of the title hydrochloride as a white solid: mp=225-227 $^{\circ}$ C; ¹H NMR (400 MHz, dmsO-d₆): 7.93-7.82 (m, 1H), 7.46-7.30 (m, 5H), 7.30-7.12 (m, 5H), 6.78 (dd, 1H, *J* = 8.8, 2.0 Hz), 5.33 (s, 2H), 3.42-3.24 (m, 2H, overlapping with H₂O),
20 3.04-2.84 (m, 3H), 2.68 (s, 3H), 2.00-1.78 (m, 4H); MS (ES⁺): *m/e* 496.9 (M+1); Calculated (for C₂₇H₂₆F₂N₂O₃S•HCl) : C 60.84, H 5.11, N 5.26; found: C 60.69, H 5.00, N 5.26.

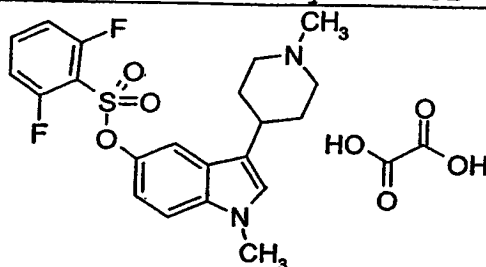
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Example 514-Fluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

5 To a solution of 3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (500 mg, 2.2 mmol) and triethylamine (333 μ L, 2.4 mmol) in THF (5mL) and DMF (5mL) was added 4-fluorobenzenesulfonyl chloride (465 mg, 2.4 mmol). The
10 reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was cooled on an ice bath and diluted with ethyl acetate. The diluted reaction mixture was washed with cold 0.2 N NaOH, cold water, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure
15 to give a white foam. The foam was crystallized from ethyl acetate to give 360 mg of a white powder. The mother liquors were purified by radial chromatography (silica gel, 2000 micron rotor, 5% methanol and 0.5% ammonium hydroxide in methylene chloride then 10% methanol and 0.5% ammonium
20 hydroxide in methylene chloride) to give 297 mg (78%) total yield of a clear oil. The oil was crystallized from ethyl acetate/hexanes to give a white powder: mp 170-172 $^{\circ}\text{C}$; MS(m/e): 388 (M^+); Calculated for $\text{C}_{20}\text{H}_{21}\text{FN}_2\text{O}_3\text{S}$: C, 61.84; H, 5.45; N, 7.21. Found: C, 62.13; H, 5.58; N, 7.25.

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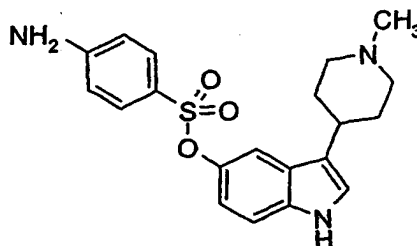
-86-

Example 522,6-Difluorobenzenesulfonic acid 1-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

5 A solution of 2,6-difluorobenzenesulfonyl chloride (312 mg, 1.47 mmol) in methylene chloride (2 mL) was added to a solution of 1-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (327 mg, 1.34 mmol) and triethylamine (226 μ L, 1.6 mmol) in tetrahydrofuran (10 mL), methylene chloride (2 mL) and DMF (6 mL). The reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with water and ethyl acetate, basified with saturated NaHCO_3 , and extracted with ethyl acetate. The ethyl acetate extracts
10 were washed with water, brine, dried (NaSO_4), filtered and concentrated under reduced pressure to give 550 mg of a white solid. The product was purified by flash chromatography (silica gel, 5%, 10% 2M ammonia in methanol/methylene chloride) to give 440 mg (78%) of
15 homogeneous title compound as a white foam. The product was crystallized as the oxalic acid salt from ethyl acetate to give a white powder: mp=195-198 $^{\circ}\text{C}$ dec; MS(m/e): 421 (M+1); Calculated for $\text{C}_{21}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_3\text{S}\cdot\text{C}_2\text{H}_2\text{O}_4$: C, 54.11; H, 4.74; N, 5.49. Found: C, 53.86; H, 4.62; N, 5.29.

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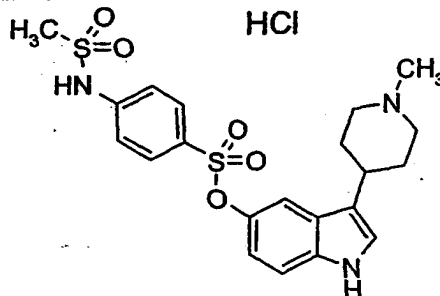
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Example 534-Aminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

5

A mixture of 4-nitrobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester (800 mg, 1.92 mmol) and 5% palladium on carbon (230 mg) in ethanol (100 mL) was hydrogenated at atmospheric pressure at ambient temperature for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10,11,12,15% 2M ammonia in methanol/methylene chloride) to give 580 mg (78%) of homogeneous product as a yellow oil that crystallized upon standing: mp=217-219 °C dec; MS(m/e): 386 (M+1), 384 (M-1); Calculated for C₂₀H₂₃N₃O₃S: C, 62.32; H, 6.01; N, 10.90. Found: C, 62.30; H, 5.91; N, 10.69.

20

Example 544-Methylsulfonylaminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride

Methylsulfonyl chloride (130 µL, 1.68 mmol) was added dropwise to a solution of 4-aminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester (480 mg, 1.25

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mmol) and diisopropylethylamine (434 μ L, 2.49 mmol) in THF (20 mL) and stirred at ambient temperature for 1 h. The reaction mixture was stored at 5 °C for 18 h. The THF solution was decanted from the yellow glass that had formed.

5 The yellow glass was dissolved in ethyl acetate and water. The ethyl acetate layer contained unreacted starting material and was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 330 mg of 4-aminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester. The aqueous layer was basified with 1N NaOH and was extracted with ethyl acetate. The ethyl acetate extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 79 mg of crude product. The crude product was purified by radial

10 chromatography (silica gel, 1000 micron rotor, 5%-20% methanol/1% ammonium hydroxide/methylene chloride) to give 51 mg (8.8%) of homogeneous product as a clear foam. Methylsulfonyl chloride (73 μ L, 0.94 mmol) was added to a solution of the recovered 4-aminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester (330 mg, 0.86

20 mmol) and pyridine (76 μ L, 0.94 mmol) in methylene chloride (10 mL) and dimethylformamide (2 mL). The reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated onto silica gel under reduced

25 pressure and purified by flash chromatography (silica gel, 5%-15% 2M ammonia in methanol/methylene chloride) to give 210 mg of a yellow solid. This product was repurified by radial chromatography (silica gel, 2000 micron rotor, 10% methanol/1% ammonium hydroxide/methylene chloride) to give

30 62 mg (16%) of homogeneous product as a yellow film. Both lots of the product (4-methylsulfonylaminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester) were combined and crystallized as the hydrochloric acid salt from ethyl acetate to give 91 mg of the title compound as a white

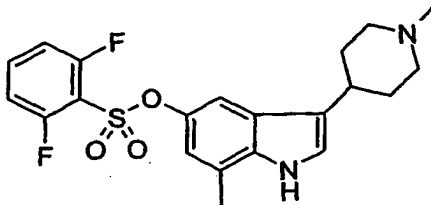
35 powder: mp=238 °C dec; MS(m/e): 464 (M+1), 462 (M-1);

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Calculated for $C_{21}H_{25}N_3O_5S_2 \cdot HCl$: C, 50.44; H, 5.24; N, 8.40.
Found: C, 50.04; H, 5.18; N, 8.19.

Example 55

5 2,6-Difluorobenzenesulfonic acid 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

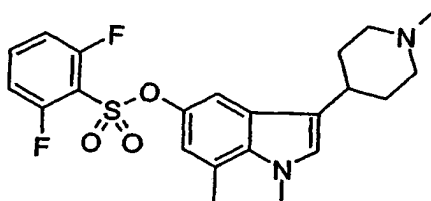


By a method similar to Example 31, using 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indole-5-ol (3.1 mmol, 0.756 g),
10 tetrahydrofuran (10 mL), 0.2N sodium hydroxide (3.1 mmol, 15.5 mL) and 2,6-difluorobenzenesulfonyl chloride (3.7 mmol, 0.7895 g) in tetrahydrofuran (10 mL) afforded the title compound as a fractional salt of 2,6-difluorobenzene sulfonic acid. The material was dissolved in methanol and 5N
15 sodium hydroxide (1 eq) was added. The mixture was then applied to a Mega Bond Elute SCX column. The column was treated with one column volume of the following: methylene chloride, methanol, 3:1 methylene chloride:methanol. The product was eluted with 3:1 methylene chloride: 2M ammonium
20 in methanol. Fractions containing the title compound were concentrated in vacuo to an oil. The oil was dissolved in diethyl ether, then placed in freezer (approximately -4 °C). The resulting crystals were collected by filtration to afford 0.296 g of the title compound. The filtrate was
25 concentrated in vacuo and resubjected to SCX chromatography as described above. An additional 0.313 g of material was collected. A total of 0.609 g (47%) of the title compound was isolated: MS (ion spray): $m/z = 421(M+1)$; 1H NMR(DMSO $_d_6$): 11.04 (s, 1H), 7.90 (m, 1H), 7.40 (m, 2H), 7.16 (1H), 6.88 (1H), 6.69 (1H), 2.78 (m, 2H), 2.54 (m, 1H), 2.39 (s, 3H),
30 2.19 (s, 3H), 1.94 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H);
Calculated for $C_{21}H_{22}F_2N_2O_3S$: C, 59.99; H, 5.27; N, 6.66.
Found: C, 59.96; H, 5.21; N, 6.65.

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Example 56

2,6-Difluorobenzenesulfonic acid 1,7-dimethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



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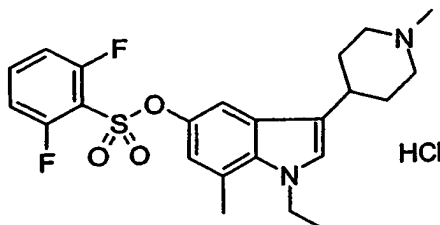
A suspension of 1,7-dimethyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (1.0 eq, 1.98 mmol, 0.511g) in THF (5.0 mL) at room temperature was added 60% sodium hydride (1.2 eq, 2.37 mmol, 0.095 g). After stirring five minutes
10 2,6-difluorobenzenesulfonyl chloride (1.1 eq, 2.18 mmol, 0.384 g) was added. The reactions were stirred at room temperature for 3 hours. The reaction was treated with water (25 mL) and 1N sodium hydroxide (2 mL) then extracted with ethyl acetate (2 x 25 mL). The organic phases were combined,
15 washed with water (25 mL) then brine (25 mL), dried over sodium sulfate, filtered and concentrated in vacuo to an oil. This material was subjected to radial chromatography, 4mm plate, eluting with 9:1 chloroform:2M ammonia in methanol. Fractions containing product were combined,
20 concentrated in vacuo to afford an oil. The title compound was crystallized from diethyl ether to afford 0.592 g (59%) of the title compound: mp=139 °C; Mass spectrum (ion spray): m/z = 439 (M+1); ¹H NMR(DMSO-d₆): 7.95-7.85 (m, 1H), 7.43-7.37 (m, 2H), 7.05 (s, 1H), 6.84 (d, J=2.20Hz, 1H), 6.64 (d, J=1.46Hz, 1H), 3.96 (s, 3H), 2.79 (m, 2H), 2.64 (s, 3H),
25 2.50-2.40 (m, 1H), 2.19 (s, 3H), 1.96 (m, 1H), 1.92 (m, 1H), 1.69-1.56 (m, 2H), 1.53 (m, 1H), 1.44 (m, 1H); Calculated for C₂₂H₂₆N₂F₂O₃S: C, 60.89; H, 5.57; N, 6.45. Found: C, 60.67; H, 5.64; N, 6.54.

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Example 57

2,6-Difluorobenzenesulfonic acid 7-methyl-1-ethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



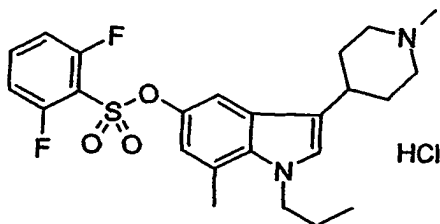
5

By a method similar to Example 56, using 1-ethyl-7-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (2.22 mmol, 0.605 g), sodium hydride (2.67 mmol, 0.107 g), and 2,6-difluorobenzenesulfonyl chloride (2.44 mmol, 0.519 g) afforded the free amine which was converted to the hydrochloride salt. Acetyl chloride (approximately 1.2 eq) was added to a cooled solution of ethanol (0°C). After stirring approximately five minutes, this solution was added to a solution of the free amine in diethyl ether. The insoluble material was collected by filtration to afford 0.844 g (78%) of the title compound: MS (ion spray): m/z = 449 (M+1); ¹H NMR (DMSO-d₆): 7.93-7.87 (m, 1H), 7.46-7.38 (m, 2H), 7.23 (s, 1H), 7.10 (d, J=1.46Hz, 1H), 6.63 (d, J=1.09Hz, 1H), 4.30 (q, 2H), 3.47-3.43 (m, 2H), 3.11-3.01 (m, 2H), 2.93-2.79 (m, 1H), 2.76 (s, 3H), 2.59 (s, 3H), 1.96-1.76 (m, 4H), 1.30 (t, J=7.14Hz, 3H); Calculated for C₂₃H₂₆F₂N₂O₃S-HCl: C, 56.96; H, 5.61; N, 5.78. Found: C, 56.97; H, 5.70; N, 5.78.

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Example 58

2,6-Difluorobenzenesulfonic acid 7-methyl-1-propyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



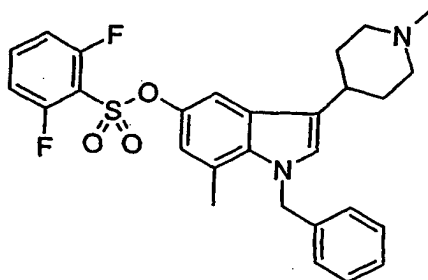
5

By a method similar to Example 56, using 1-propyl-7-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (0.619 g), sodium hydride (2.59 mmol, 0.104 g, 60% dispersion in mineral oil), and 2,6-difluorobenzenesulfonyl chloride (2.38 mmol, 0.505 g) afforded 0.589 g (55%) of the free base which was converted to the hydrochloride salt to give the title compound: MS (ion spray): $m/z = 463 (M+1)$; 1H NMR (DMSO- d_6): 7.97-7.87 (m, 1H), 7.42 (dd, $J=8.78, 3.11$ Hz, 2H), 7.22 (s, 1H), 6.63 (s, 1H), 4.22 (t, $J=7.32$ Hz, 2H), 3.49-3.39 (m, 2H), 3.13-2.93 (m, 2H), 2.90-2.79 (m, 1H), 2.76 (s, 3H), 2.50 (s, 3H), 1.97-1.78 (m, 4H), 1.68 (q, $J=14.27, 7.32$ Hz, 2H), 0.84 (t, $J=7.51$ Hz, 3H); Calculated for $C_{24}H_{28}F_2N_2O_3S \cdot HCl$: C, 57.77; H, 5.86; N, 5.61. Found: C, 57.38; H, 5.79; N, 5.58.

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Example 59

2,6-Difluorobenzenesulfonic acid 1-benzyl-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



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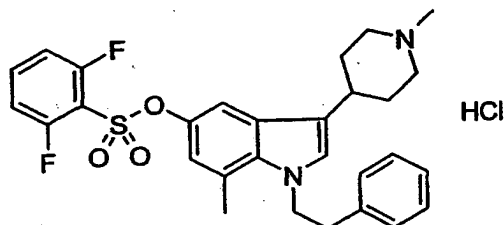
By a method similar to Example 56, using 1-benzyl-7-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (1.81

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mmol, 0.604 g) in THF (4.5 mL), sodium hydride (2.17 mmol, 0.087g, 60% dispersion in mineral oil), and 2,6-difluorobenzenesulfonyl chloride (1.99 mmol, 0.422 g) afforded 0.411 g (45%) of the title compound: mp=158 °C; mass spectrum (ion spray): m/z = 511(M+1); ¹H NMR(DMSO-d₆): 7.96-7.86 (m, 1H), 7.41 (dd, J=5.73, 3.48Hz, 2H), 7.31-7.19 (m, 4H), 6.94 (d, J=2.20Hz, 1H), 6.82 (d, J=6.59Hz, 2H), 6.62 (d, J=1.87Hz, 1H), 5.55 (s, 2H), 2.81-2.77 (m, 2H), 2.56-2.42 (m, 1H), 2.36 (s, 3H), 2.20 (s, 3H), 1.96 (m, 2H), 1.72-1.67 (m, 2H), 1.53 (m, 2H); Calculated for C₂₈H₂₈F₂N₂O₃S-0.3H₂O: C, 65.17; H, 5.59; N, 5.43. Found: C, 65.27; H, 5.47; N, 5.49.

Example 60

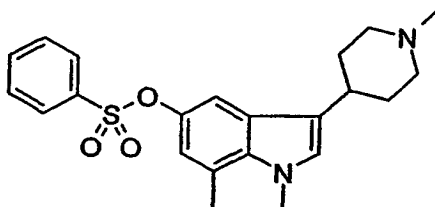
2,6-Difluorobenzenesulfonic acid 7-methyl-1-phenethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester hydrochloride



By a method similar to Example 56, using 7-methyl-3-(1-methylpiperidin-4-yl)-1-phenethyl-1H-indol-5-ol (0.55 mmol, 0.190 g) in THF (1.4 mL), sodium hydride (0.65 mmol, 0.026 g, 60% dispersion in mineral oil), and 2,6-difluorobenzenesulfonyl chloride (0.60 mmol, 0.128 g) afforded 0.136 g (44%) of the title compound: MS (ion spray): m/z = 511(M+1); ¹H NMR(DMSO-d₆): 7.97-7.87 (m, 1H), 7.45-7.38 (m, 2H), 7.29-7.17 (m, 2H), 7.13 (d, 2H), 6.63 (d, J=1.10Hz, 1H), 4.53 (t, J=7.50Hz, 2H), 3.47-3.39 (m, 2H), 3.11-2.95 (m, 4H), 2.87-2.69 (m, 4H), 2.60 (s, 3H), 1.94-1.71 (m, 4H); Calculated for C₂₈H₂₈F₂N₂O₃S-1.9 H₂O: C, 61.73; H, 5.88; N, 5.14. Found: C, 61.43; H, 5.51; N, 4.93.

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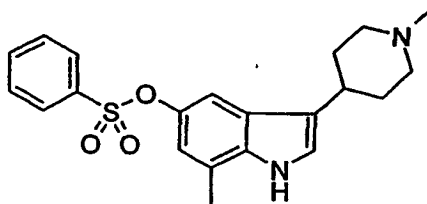
-94-

Example 61Benzenesulfonic acid 1,7-dimethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

5

By a method similar to Example 56, using 1,7-dimethyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (1.98 mmol, 0.511 g) in THF (5.0 mL), sodium hydride (2.37 mmol, 0.095 g, 60% dispersion in mineral oil), and benzenesulfonyl chloride (2.18 mmol, 0.384 g), afforded 0.501 g (64%): ms (ion spray): $m/z = 399$ ($M+1$); ^1H NMR(DMSO- d_6): 7.85-7.77 (m, 3H), 7.67-7.62 (m, 2H), 7.01 (s, 1H), 6.64 (d, $J=2.56\text{Hz}$, 1H), 6.55 (d, $J=1.83\text{Hz}$, 1H), 3.94 (s, 3H), 2.82-2.72 (bd, 2H), 2.60 (s, 3H), 2.39 (tt, $J=3.72\text{Hz}$, 1H), 2.18 (s, 3H), 1.91 (m, 2H), 1.67-1.54 (m, 2H), 1.47 (m, 2H); Calculated for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.18; H, 6.58; N, 7.08.

20

Example 62Benzenesulfonic acid 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

25

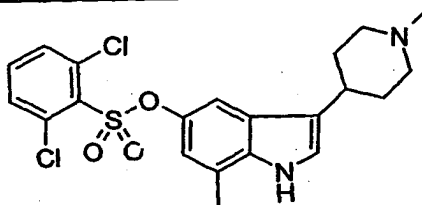
To a suspension of 1-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (2.52 mmol, 0.616 g) in THF (6.4 mL) at room temperature was added 60% sodium hydride (3.03 mmol, 0.121 g). After stirring 15 minutes, benzenesulfonyl chloride (2.77 mmol, 0.490 g) was added. Reaction stirred at room temperature for 24 hours. Reaction then treated with

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ethyl acetate (25 mL) and washed with water (2 x 25 mL) then brine (25 mL). The organic phase was dried over sodium sulfate, filtered, concentrated in vacuo to afford an oil. The oil was subjected to normal phase radial chromatography, 4mm plate eluting with 9:1 chloroform:2M ammonia in methanol. Fractions containing product combined, concentrated in vacuo to afford an oil. The oil was dissolved in diethyl ether. The solution was cooled at -4 °C which resulted in crystal formation. Crystals collected by filtration to afford 0.639g (66%) of the title compound: mp=118 °C; mass spectrum (ion spray): m/z = 385(M); ¹H NMR(DMSO-d₆): 7.85-7.77 (m, 3H), 7.67-7.62 (m, 2H), 7.12 (d, J=2.20Hz, 1H), 6.69 (d, J=2.20Hz, 1H), 6.60 (d, J=1.46Hz, 1H), 2.77-2.68 (bd, 2H), 2.43 (m, 1H), 2.37 (s, 3H), 2.19 (s, 3H), 1.92 (m, 2H), 1.71-1.62 (m, 2H), 1.52 (m, 2H); Calculated for C₂₁H₂₄N₂O₃S: C, 65.60; H, 6.29; N, 7.29. Found: C, 65.64; H, 6.45; N, 7.19.

Example 63

2,6-Dichlorobenzenesulfonic acid 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester



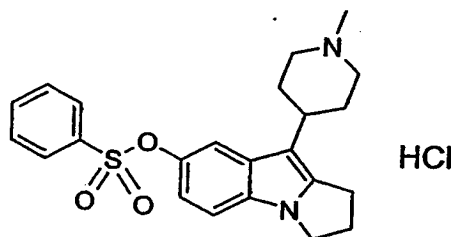
By a method similar to Example 62, using 1-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (2.54 mmol, 0.620 g), sodium hydride (3.04 mmol, 0.122 g, 60% dispersion in mineral oil), and 2,6-dichlorobenzenesulfonyl chloride (2.79 mmol, 0.685 g) afforded the title compound which crystallized at room temperature to afford 0.845 g (73%) of the title compound: mp=179 °C; MS (ion spray): m/z = 453(M), 455 (M+2); ¹H NMR(DMSO-d₆): 7.77-7.68 (m, 3H), 7.14 (d, J=1.46Hz, 1H), 6.87 (d, J=1.83Hz, 1H), 6.70 (d, J=1.10Hz, 1H), 2.84-2.77 (bd, 2H), 2.50 (m, 1H), 2.38 (s, 3H), 2.20 (s, 3H), 1.95 (m, 2H), 1.72-1.63 (m, 2H), 1.59-1.46 (m, 2H);

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Calculated for $C_{21}H_{22}ClN_2O_3S$: C, 55.63; H, 4.89; N, 6.18.
Found: C, 55.48; H, 4.87; N, 6.12.

Example 64

5 Benzenesulfonic acid 9-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-yl ester hydrochloride

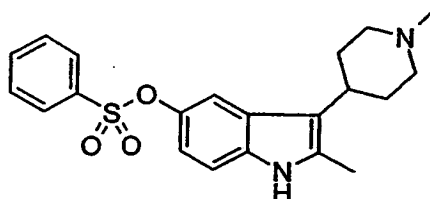


By a method similar to Example 31, using 9-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-ol (135 mg, 0.5 mmol), NaOH (3.25 mL, 0.65 mmol, 0.2 N), benzenesulfonyl chloride (99 mg, 0.564 mmol), and THF (1.5 mL) gave a crude residue which was purified by PCTLC (silica gel GF rotor; 95:5 $CHCl_3$:2M NH_3 in MeOH) and the hydrochloride was formed in EtOAc affording 196 mg (88%) of the title compound as an off-white powder: mp=202-204 °C; MS (ES+): m/e 411.0 (M+1); Calculated for $C_{23}H_{26}N_2O_3SHCl$: C, 61.80; H, 6.09; N, 6.27. Found: C, 61.49; H, 6.10; N, 6.27.

20

Example 65

Benzenesulfonic acid 2-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

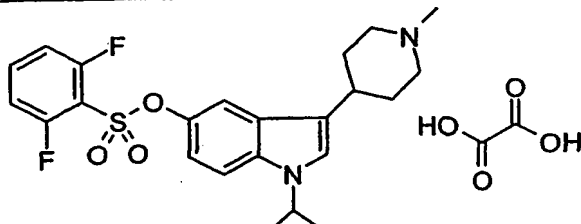


By a method similar to Example 31, using 2-methyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-1H-indole (250 mg, 1.03 mmol), benzenesulfonyl chloride (0.22 g, 1.25 mmol), 0.2N sodium hydroxide and THF (2 mL) gave 96 mg (24%) of the title compound: mass spectrum (ES+)= 385.1.

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Example 66

2,6-Difluorobenzenesulfonic acid 1-isopropyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate



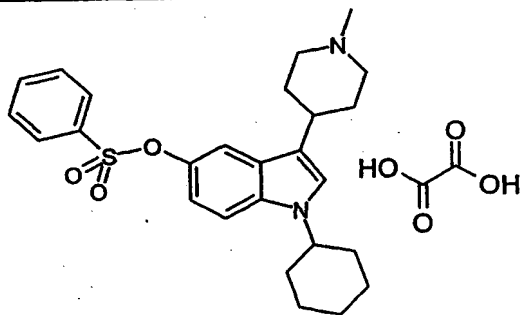
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By a method similar to Example 27, using 2,6-Difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester (400mg, 0.98mmol), isopropyl tosylate (2.11g, 0.8 mmol) and dimethylformamide (20 mL) and sodium hydride (60% dispersion in mineral oil, 43 mg, 1.08 mmol) to afford 54 mg (12%) of the free base of the title compound which was converted to the oxalic salt (58mg): mp=248-251 °C.

15

Example 67

Benzenesulfonic acid 1-cyclohexyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester oxalate

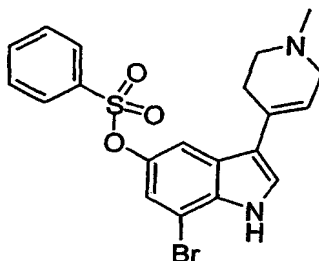


By a method similar to Example 27, using benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester (400 mg, 1.07 mmol), toluene-4-sulfonic acid cyclohexyl ester (2.75 g, 10.7 mmol) and dimethylformamide (20 mL) and sodium hydride (60% dispersion in mineral oil, 47 mg, 1.18 mmol) to afford 189 mg (39%) of the free base of the title compound which was converted to the oxalic salt (110 mg): mp=96-102 °C.

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Example 68

Benzenesulfonic acid 7-bromo-3-(1-methyl-1,2,3,6-tetrahydro-
pyridin-4-yl)-1H-indol-5-yl ester



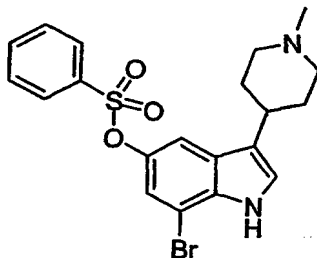
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Combine benzenesulfonic acid 7-bromo-1H-indole-5-yl ester and 1-methyl-4-piperidone (4 eq.) in acetic acid. Heat to about 75°C before adding 2.0 N H₃PO₄ (3 eq.). After about 6 hours, cool to room temperature and pour into a mixture of ammonium hydroxide in ice water. Separate the organic layer and dry over Na₂SO₄ and concentrated. Purify to give the title compound.

10

Example 69

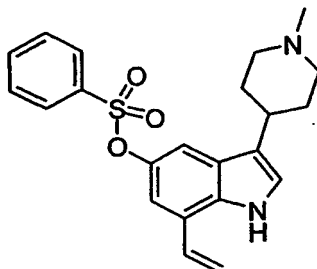
Benzenesulfonic acid 7-bromo-3-(1-methylpiperidin-4-yl)-1H-
indol-5-yl ester



A method similar to Preparation 20, using benzenesulfonic acid 7-bromo-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester gives the title compound.

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Example 70Benzenesulfonic acid 7-vinyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester

5 A mixture of benzenesulfonic acid 7-bromo-3-(1-methylpyridin-4-yl)-1H-indol-5-yl ester and $\text{Pd}(\text{PPh}_3)_4$ (0.2 eq.) in dry toluene was degassed and then treated with vinyl tributyltin (1.1 eq.). Heat the reaction mixture to reflux.
10 After 5 hours, cool to room temperature, pour into ethyl acetate, wash with brine, dry the organic layer over Na_2SO_4 , and concentrate. Purify to give the title compound.

The compounds of the present invention can be administered alone or in the form of a pharmaceutical
15 composition, that is, combined with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. The
20 compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable salts, for purposes of stability, convenience, solubility, and the like. In practice, the compounds of formula I are usually
25 administered in the form of pharmaceutical compositions, that is, in admixture with pharmaceutically acceptable carriers or diluents.

Thus, the present invention provides pharmaceutical compositions comprising a compound of the formula I and a
30 pharmaceutically acceptable diluent.

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The compounds of formula I can be administered by a variety of routes. In effecting treatment of a patient afflicted with disorders described herein, a compound of formula I can be administered in any form or mode which
5 makes the compound bioavailable in an effective amount, including oral and parenteral routes. For example, compounds of formula I can be administered orally, by inhalation, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, occularly, topically,
10 sublingually, buccally, and the like. Oral administration is generally preferred for treatment of the disorders described herein.

One skilled in the art of preparing formulations can readily select the proper form and mode of administration
15 depending upon the particular characteristics of the compound selected, the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances. (*Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (1990)).

20 The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known
25 in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the like.

30 The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of
35 tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present

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invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention may be determined by a person skilled in the art.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations typically contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 90% of the weight thereof. The amount of the compound of formula I present in such compositions is such that a suitable dosage will be obtained. The solutions or suspensions may also include one or more of the following

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adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Preferred compositions and preparations are able to be determined by one skilled in the art.

The compounds of the present invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment, or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bees wax, mineral oil, diluents such as water and alcohol, and emulsifiers, and stabilizers. Topical formulations may contain a concentration of the formula I or its pharmaceutical salt from about 0.1 to about 10% w/v (weight per unit volume).

The compounds of formula I are antagonists of 5-HT₆ receptors. Moreover the compounds of formula I are selective antagonists of that particular serotonin receptor. Such antagonism can be identified by the methods below.

Example A

Assay description for 5HT₆ binding

The assay buffer used is 50 mM Tris-HCl pH 7.4, 120 mM NaCl, 5 mM KCl, 5 mM MgCl₂, 1 mM EDTA. The radioligand used is ³H - LSD from New England Nuclear Cat. # NET 638 - 75.9 Ci/mmol. The membranes used are from Receptor Biology, Cat. No. RB-HS6. These are membranes from HEK-293 cells expressing the Human 5HT₆ receptor.

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Test compounds are obtained as 10 mM stocks in 100% DMSO. They are diluted to 1 mM in 100% DMSO by adding 180 μ l DMSO to 20 μ l of stock in 96 well plates using a multidrop. The 1 mM stocks are then diluted to make an 11 point concentration range from 125 μ M down to 1.25 nM in half log increments using 10% DMSO as diluent. This is done using a TECAN robot. The final DMSO at this stage is 21.25%.

Radioligand is diluted in assay buffer to make a 125 nM solution and each vial of membranes is diluted up to 92 mL in assay buffer. The final assay volume is 250 μ l consisting of 210 μ l of diluted membranes, 20 μ l of compound or 21.25% DMSO for total binding, and 20 μ l of diluted radioligand. The compounds are transferred from drug dilution plates into corning 96 well assay plates using a 96 well Multimek pipettor. Radioligand and membranes are added to assay plates using multidrop pipettors. Non-specific binding is determined in wells containing a final serotonin concentration of 10 μ M. In the final assay volume the radioligand is 10 nM and the membrane protein is approximately 25 μ g/well. The final drug concentration range in half logs is from 10 μ M down to 0.1 nM. The final DMSO in the assay is 1.7%.

After addition of drug, membrane, and ligand, the plates are incubated for one hour at room temperature. During this time 96 well Millipore filter plates (MAFBN0B50) are soaked for a least 30 minutes with 200 μ l per well of 0.5% polyethyleneimine.

The 0.5% PEI is removed from filterplate wells using a TiterTek MAP aspirator and 200 μ l of the incubation mixture is transferred from the incubation plate to the filterplate after mixing. This transfer is done using the 96 tip Mutimek pipettor. After transfer to the filterplate filterplates are extracted and washed twice with 220 μ l per well of cold buffer on the MAP aspirator. The peel away bottoms are removed from the filterplates and 100 μ l per well of microscint 20 scintillation fluid is added per well using a multidrop. Plates are placed into suitable holders and are

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left at room temperature for three hours and are counted for ^3H in either a Wallac Microbeta counter or on a Packard Topcount.

5 In one embodiment, the present invention provides methods of treating disorders associated with the 5-HT₆ receptor, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. Thus, the present invention contemplates the various disorders described to be treated herein and others which
10 can be treated by such antagonists as are appreciated by those skilled in the art.

In particular, because of their ability to antagonize the 5-HT₆ receptor, it is recognized that the compounds of the present invention are useful for treating cognitive
15 disorders, that is, disorders involving cognitive deficits. A number of the disorders which can be treated by 5-HT₆ antagonists are known according to established and accepted classifications, while others are not.

Some of the disorders to be treated according to the
20 present invention are not well categorized and classified because cognition is a complicated and sometimes poorly defined phenomenon. It is, however, widely recognized that cognition includes various "domains." These domains include short term memory, long term memory, working memory,
25 executive function, and attention.

While many of the disorders which can be treated according to the present invention are not uniformly described and classified in the art, it is understood that the compounds of the present invention are useful for
30 treatment of disorders characterized by a deficit in any of the cognitive domains listed above or in other aspects of cognition. Thus the term "cognitive disorders" is meant to encompass any disorder characterized by a deficit in one or more cognitive domain, including but not limited to short
35 term memory, long term memory, working memory, executive function, and attention.

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One cognitive disorder to be treated by the present invention is age-related cognitive decline. This disorder is not well defined, but includes decline in the cognitive domains, particularly the memory and attention domains, which accompany aging. Another is mild cognitive impairment. Again, this disorder is not well defined in the art, but involves decline in the cognitive domains, and is believed to represent a group of patients the majority of which have incipient Alzheimer's disease. Also, a wide variety of insults, including stroke, ischemia, hypoxia, inflammation, and infectious processes can result in cognitive deficits as a sequella which can be treated according to the present invention.

Where the disorders which can be treated by 5-HT₂ antagonists are known according to established and accepted classifications, these classifications can be found in various sources. For example, at present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool for identifying many of the disorders described herein. Also, the International Classification of Diseases, Tenth Revision, (ICD-10) provides classifications for many of the disorders described herein. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for disorders described herein, including those as described in the DMS-IV and ICD-10, and that terminology and classification systems evolve with medical scientific progress.

In one embodiment, the present invention provides methods of treating disorders selected from the group consisting of: age-related cognitive disorder, mild cognitive impairment, mood disorders (including depression, mania, bipolar disorders), psychosis (in particular schizophrenia), anxiety (particularly including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), idiopathic and drug-induced Parkinson's disease,

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epilepsy, convulsions, migraine (including migraine headache), substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, conduct disorder, learning disorders, dementia (including Alzheimer's disease and AIDS-induced dementia), Huntington's Chorea, cognitive deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage, vascular dementia, multi-infarct dementia, amyotrophic lateral sclerosis, and multiple sclerosis, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. That is, the present invention provides for the use of a compound of formula I or pharmaceutical composition thereof for the treatment disorders associated with the 5-HT₆ receptor.

It is recognized that the terms "treatment" and "treating" are intended to include improvement of the cognitive deficit associated with each of the disorders associated with the 5-HT₆ receptor described herein. Also, it is also recognized that one skilled in the art may affect the disorders by treating a patient presently afflicted with the disorders or by prophylactically treating a patient believed to be susceptible to such disorders with an effective amount of the compound of formula I. Thus, the terms "treatment" and "treating" are intended to refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the disorders described herein, but does not necessarily indicate a total elimination of all symptoms, and is intended to include prophylactic treatment of such disorders. For example, the present invention specifically encompasses the treatment of the cognitive deficits associated with schizophrenia, stroke, Alzheimer's disease, and the other disorders described herein. Thus, it is

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understood that the present invention includes adjunctive treatment of the disorders described herein. More specifically, the compounds of formula I are useful to treat schizophrenia in combination with typical and atypical antipsychotics; to treat stroke in combination with a variety of agents such as mGluR agonists, NMDA antagonists, IL 1-6 inhibitors, and the like; to treat Alzheimer's disease in combination with cholinergics, including cholinesterase inhibitors, and compounds that inhibit amyloid protein processing.

As used herein, the term "patient" refers to a warm blooded animal such as a mammal which is afflicted with one or more disorders associated with the 5-HT₆ receptor. It is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, pigs, and humans are examples of animals within the scope of the meaning of the term. It is also understood that this invention relates specifically to the antagonists of the 5-HT₆ receptor.

As used herein, the term "effective amount" of a compound of formula I refers to an amount, that is, the dosage which is effective in treating the disorders described herein.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining an effective amount, the dose of a compound of formula I, a number of factors are considered by the attending diagnostician, including, but not limited to: the compound of formula I to be administered; the co-administration of other therapies, if used; the species of mammal; its size, age, and general health; the specific disorder involved; the degree of involvement or the severity of the disorder; the response of the individual patient; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use

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of other concomitant medication; and other relevant circumstances.

An effective amount of a compound of formula I is expected to vary from about 0.1 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts are able to be determined by one skilled in the art.

Of the disorders to be treated according to the present invention a number are particularly preferred.

10 In a preferred embodiment the present invention provides a method of treating cognitive disorders, comprising: administering to a patient in need thereof an effective amount of a compound of Claim 1.

15 In another preferred embodiment the present invention provides a method for treating Alzheimer's disease, comprising: administering to a patient in need thereof an effective amount of a compound of formula I.

20 In a preferred embodiment the present invention provides a method for treating schizophrenia, comprising: administering to a patient in need thereof an effective amount of a compound of formula I.

25 The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including schizophrenia and related disorders.

30 In a preferred embodiment the present invention provides a method for treating migraine, comprising: administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof.

35 In one of the available sources of diagnostic tools, *Dorland's Medical Dictionary* (23rd Ed., 1982, W. B. Saunders Company, Philadelphia, PA), migraine is defined as a symptom complex of periodic headaches, usually temporal and unilateral, often with irritability, nausea, vomiting, constipation or diarrhea, and photophobia. As used herein

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the term "migraine" includes to these periodic headaches, both temporal and unilateral, the associated irritability, nausea, vomiting, constipation or diarrhea, photophobia, and other associated symptoms. The skilled artisan will

5 recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, including migraine, and that these systems evolve with medical scientific progress.

In a preferred embodiment the present invention
10 provides a method for treating anxiety disorders, including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder, comprising: administering to a patient in need thereof an effective amount of a compound of formula I.

15 At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including anxiety and related disorders. These include: panic disorder with or without
20 agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety
25 disorder and anxiety disorder not otherwise specified. As used herein the term "anxiety" includes treatment of those anxiety disorders and related disorder as described in the DSM-IV. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification
30 systems for neurological and psychiatric disorders, and particular anxiety, and that these systems evolve with medical scientific progress. Thus, the term "anxiety" is intended to include like disorders that are described in other diagnostic sources.

35 A number of preclinical laboratory animal models have been described for the disorders described herein.

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Example BAnimal Model of Dural Protein Extravasation

Harlan Sprague-Dawley rats (250-350 g) were anesthetized with sodium pentobarbital intraperitoneally (65 mg/kg) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm. Following a midline sagittal scalp incision, two pairs of bilateral holes were drilled through the skull (6 mm posteriorly, 2.0 and 4.0 mm laterally, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc.), were lowered through the holes in both hemispheres to a depth of 9 mm.

The femoral vein was exposed and a dose of the test compound was injected intravenously (i.v.) at a dosing volume of 1 mL/kg or, in the alternative, test compound was administered orally (p.o.) via gavage at a volume of 2 mL/kg. Approximately 8 minutes post i.v. injection, a 50 mg/kg dose of Evans Blue, a fluorescent dye, was also injected intravenously. The Evans Blue complexed with proteins in the blood and functioned as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion was stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research).

Fifteen minutes following stimulation, the animals were killed and exsanguinated with 40 mL of saline. The top of the skull was removed to facilitate the collection of the dural membranes. The membrane samples were removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues were coverslipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer was used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm was utilized

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and the emission intensity at 600 nm was determined. The microscope was equipped with a motorized stage and also interfaced with a personal computer. This facilitated the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 nm steps) on each dural sample. The mean and standard deviation of the measurements were determined by the computer.

The extravasation induced by the electrical stimulation of the trigeminal ganglion was an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion was stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side, over the amount of extravasation in the unstimulated side, was calculated. Control animals dosed only with saline, yielded a ratio of approximately 1.9. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side would yield a ratio of approximately 1.0.

The fear potentiated startle response model has been extensively used as a model of anxiety and can be used to evaluate the present compounds. Davis, *Psychopharmacol.*, 62: 1 (1979); Davis, *Behav. Neurosci.*, 100: 814 (1986); Davis, *Tr. Pharmacol. Sci.*, 13: 35 (1992).

Example C

Fear Potentiated Startle Paradigm

Male Sprague-Dawley rats weighing 325-400 g were purchased from Harlan Sprague-Dawley, Inc. (Cumberland, IN) and given a one week acclimation period before testing. Rats were individually housed with food and water ad libitum in an animal room on a 12-hour light/dark cycle with lights on between 6:00 A.M. and 6:00 P.M. The compound of Example 16 was prepared in a suspension of 5% ethanol, 0.5% CMC, 0.5% Tween 80 and 99% water. 2S-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl) propionic acid was

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prepared in sterile water. Control rats were given the respective vehicle.

The fear potentiated startle paradigm is conducted over three consecutive days. All three days begin with a 5-minute adaptation period before the trial starts. On day one (baseline startle) after the adaptation period, the animal receives 30 trials of 120dB auditory noise. The mean startle amplitude (V_{max}) is used to assign animals to groups with similar means before conditioning begins. Day two consists of conditioning the animals. Each animal receives 0.5 mA of shock for 500 msec preceded by a 5 second presentation of light which remains on for the duration of the shock. Ten presentations of the light and shock are administered. Day three is the testing trial where drug administration occurs prior to testing. Twenty-four hours after conditioning, startle testing sessions are conducted. Ten trials of acoustic startle (120 dB), non-light paired, are presented at the beginning of the session. This is followed by 20 random trials of the noise alone and 20 random trials of noise preceded by light. Excluding the first 10 trials, the startle response amplitudes for each trial type are averaged for each animal. Data is presented as the difference between light + noise and noise-alone. Differences in startle response amplitudes were analyzed by JMP statistical software using a One-way Anova (analysis of variance, t-test). Group differences were considered to be significant at $p < 0.05$.

The radial arm maze model can be used as a model of cognition and can be used to evaluate the present compounds.

Example D

Radial Arm Maze

The delayed non-match to sample task has been used to study the effect of drugs on memory retention (Pussinen, R. and Sirvio, J. *J of Psychopharm* 13: 171-179(1999); Staubli, U., et al. *Proc Natl Acad Sci* 91: 777-781(1994)) in the eight arm radial maze.

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Well-trained rats were allowed to retrieve food rewards from four randomly selected arms of the maze (sampling phase). Some time later, the rats were exposed to eight open arms and were tested for their ability to remember and avoid the arms they had previously entered to obtain food. Re-entry into an arm that was baited during the sampling session was counted as a reference error, whereas entry into the same arm more than once during the retention session was counted as working error. The total (reference + working) number of errors made during the retention test increases with increasing delay periods. For example, young male rats made 0.66 (+ 0.4) errors at a 1 minute delay, 2 (+ 0.5) errors at a one hour delay, and 3.95 (+ 0.2) errors at a seven hour delay (observations of this lab).

Male Sprague-Dawley rats were individually housed and maintained on a 12h light-dark cycle (lights on at 6 am). The rats were given free access to water and maintained at 85% of their free-feeding weight by supplemental feedings of Purina Lab Chow.

The rats were initially trained to search for food at the end of each of the eight arms. Once the rats had reached the criteria of no more than two errors (i.e. entering the same arm more than once during a session) on three consecutive days, a delay of one minute was imposed between the fourth and the fifth arm choices. This training ensured that the rats were thoroughly familiar with the procedural aspects of the task before any drugs were administered. Once stable performance had been obtained on the delay task (i.e. no more than one error was made on three consecutive days), drug and vehicle tests commenced using a seven hour delay period. A novel set of arms was baited each day for each rat and the maze was thoroughly cleaned during the delay period.

During the sampling session, each rat was placed on the center platform with access to all eight arms of the maze blocked. Four of the eight arms were randomly selected and baited with food. The gates of the baited arms were raised and the rat was allowed five minutes to obtain the food at

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the end of each of the four arms. As soon as the rat had obtained the food, it was removed, administered vehicle or various doses of compounds, and placed back in its home cage. Seven hours later (retention session), the rat was placed back onto the center platform with access to all eight arms blocked. The four arms that were previously baited during the sampling session, were baited and the gates to all eight arms were raised. The rat was allowed five minutes to obtain the remaining four pieces of food. An entry into a non-baited arm or a re-entry into a previously visited arm was counted as an error. Significance ($p < 0.05$) was determined using a repeated measure ANOVA followed by a Dunnett's test for comparison with control.

In order to compare test compounds with standards, scopolamine and tacrine were administered s.c. immediately after the sampling phase. The effects of scopolamine, a known amnesic, were tested after a three-hour delay, whereas the effect of tacrine, a cholinesterase inhibitor used in the treatment of Alzheimer's disease was tested after a six-hour delay. Scopolamine disrupted retention after a three-hour delay in a dose-related fashion. Tacrine significantly improved retention after a six-hour delay at 10, but not at 3 mg/kg.

25

Example E

Acquisition in the Radial Maze 8-arm radial maze acquisition

A prominent early feature of Alzheimer's disease (AD) symptomology is a pronounced deficit in declarative memory (R.W. Parks, R.F. Zec & R.S. Wilson (Eds.), *Neuropsychology of Alzheimer's disease and other dementias*. NY: Oxford University Press pp. 3-80 (1993)).

As the disease progresses, other domains of cognition become severely affected as well. Among the brain regions affected early in the progression of AD is the hippocampus, which is a critical neural substrate for declarative memory (West M.J., Coleman P.D., Flood D.G. & Troncoso J.C..

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Differences in the pattern of hippocampal neuronal loss in normal aging and Alzheimer's disease. *Lancet*, 344: 769-772(1994). One behavioral test that is often used to assess hippocampal function in animal models is the 8-arm radial maze (Olton D.S. The radial arm maze as a tool in behavioral pharmacology. *Physiology & Behavior*, 40: 793-797 (1986)).

Lesions or pharmacological blockade of the hippocampus disrupt performance of this task. Moreover, aged animals generally show deficits in this task (Porsolt R.D., Roux S. & Wettstein J.G. Animal models of dementia. *Drug Development Research*, 35: 214-229(1995)).

In this test of spatial learning and memory, a hungry rat is placed in the center of the maze and allowed to traverse the maze in search of food located at the end of each runway arm. In this version of the maze, the rat learns a win-shift strategy in which a visited arm is not replaced. Therefore, the most efficient foraging strategy is to visit each arm once. The version of the maze also taps into general learning processes as the rat is naïve to the maze on day one of the four day experiment.

Upon arrival, male Sprague Dawley®, rats were individually housed in a regular light-cycle colony room and allowed to acclimate for at least 4 days prior to testing. Each rat was reduced to and maintained at 85% of their target body weight throughout the experiment. Proper body weight was maintained by adjusting the allotment of lab chow based on a combination of age and the rat's daily bodyweight reading.

A session began with an individual rat being placed into the hub of the maze and then all guillotine doors were raised, allowing free access to all areas of the maze. A food hopper was located at the end of each of the 8 runway arms and a single food pellet was placed in each food hopper. Each daily session terminated when either all 8 food-hoppers had been visited or when the rat timed out (15 min on Day 1: 5 min on Days 2-4). The number of arm entries was recorded. Errors were counted as repeat arm entries or

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failures to visit an arm in the session period. An animal was excluded from the study if it failed to visit at least one arm on Day 1, 2 arms on Day 2, and at least 4 arms on Days 3 & 4.

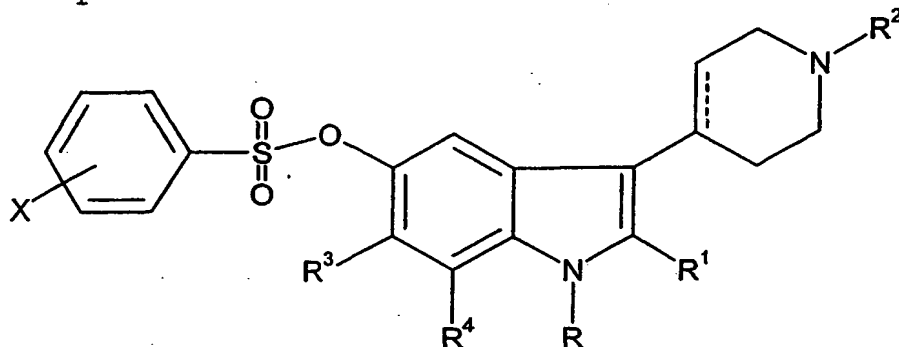
5 Each rat was pseudo-randomly assigned to either a vehicle or drug group and received the same treatment throughout the experimental period. Vehicle consisted of 5% acacia within sterile water. Injections were administered subcutaneously 20-30 minutes prior to each daily session.

10 In this acquisition task, vehicle-treated animals do not consistently show significant acquisition of maze learning as compared to the number of errors committed on Day 1. We have found that in compounds that facilitate acquisition of maze learning, the effects are often not
15 observed until the fourth day of training. Therefore, results consisted of total Day 4 errors across treatment groups.

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WHAT IS CLAIMED IS:

1. A compound of the formula



wherein

R is hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkylsulfonyl, phenylsulfonyl, substituted phenylsulfonyl, naphthylsulfonyl, benzylsulfonyl, or substituted benzylsulfonyl;

R¹ is hydrogen or C₁-C₃ alkyl or where R⁴ is hydrogen, C₁-C₆ alkyl, or halo then R¹ and R may be taken together to form -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂-;

R² is hydrogen or C₁-C₆ alkyl;

R³ is hydrogen or halo;

R⁴ is hydrogen, C₁-C₆ alkyl, vinyl, allyl, C₂-C₆ alkynyl, or halo or when R¹ is hydrogen or C₁-C₃ alkyl then R⁴ and R may be taken together to form -CH₂-CH₂-CH₂-;

X is 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, nitro, amino, C₁-C₆ alkylsulfonylamino, and cyano or X is 5 halo substituents;

||

represents either a single or a double bond;

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and pharmaceutically acceptable addition salts thereof.

2. A compound according to Claim 1 wherein R is hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl.

5 3. A compound according to Claim 2 wherein R is hydrogen or C₁-C₆ alkyl.

4. A compound according to Claim 3 wherein R¹ is hydrogen or C₁-C₃ alkyl.

10 5. A compound according to Claim 1 wherein R and R¹ are taken together to form -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂.

6. A compound according to Claim 1 wherein R and R⁴ are taken together to form -CH₂-CH₂-CH₂-.

15 7. A compound according to anyone of Claims 2-6 wherein R² is C₁-C₆ alkyl.

8. A compound according to anyone of Claims 2-6 wherein R² is methyl.

9. A compound according to A compound according to anyone of Claims 2-8 wherein X is halo.

20 10. A compound according to Claim 9 wherein X is fluoro.

11. A compound according to Claim 10 wherein X is 2,6-difluoro.

25 12. A compound of Claim 1 selected from the group consisting of

Benzenesulfonic acid 1-propyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester,

Benzenesulfonic acid 1-benzyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

30 2,6-Difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1-propyl-1H-indol-5-yl ester,

Benzenesulfonic acid 1-ethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

35 Benzenesulfonic acid 1-propyl-3-(1-methylpyridin-4-yl)-1H-indol-5-yl ester,

Benzenesulfonic acid 1-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

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- 2,6-Difluorobenzenesulfonic acid 1-ethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
2,6-Difluorobenzenesulfonic acid 1-benzyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
5 Benzenesulfonic acid 1-benzyl-3-(1-methylpiperidin-4-yl)-1-phenethyl-1H-indol-5-yl ester,
Benzenesulfonic acid 1-(3-phenylpropyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-(propylsulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
10 Benzenesulfonic acid 1-(isopropylsulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-ethylsulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
15 Benzenesulfonic acid 1-methylsulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-benzylsulfonyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-(naphth-1-ylsulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
20 Benzenesulfonic acid 1-butyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-(4-Fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
25 Benzenesulfonic acid 1-(2,4-difluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-(2-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-(3-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
30 Benzenesulfonic acid 1-isobutyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
Benzenesulfonic acid 1-cyclohexylmethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
35 Benzenesulfonic acid 1-(4-phenylbutyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

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- Benzenesulfonic acid 1-(pyrid-2-ylmethyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- Benzenesulfonic acid 1-(2,2,2-trifluoroethyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 5 Benzenesulfonic acid 1-isopropyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- Benzenesulfonic acid 1-cyclopentyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 10 Benzenesulfonic acid 1-butyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- Benzenesulfonic acid 1-(4-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 2,6-difluorobenzenesulfonic acid 2-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 15 2,6-Difluorobenzenesulfonic acid 6-fluoro-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 2,6-Difluorobenzenesulfonic acid 9-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-yl ester,
- Benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 20 2,4-Difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 4-Iodobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 25 4-Chlorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 4-Methoxybenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 4-Methylphenylsulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 30 2-Fluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 2,3,4-Trifluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,
- 35 4-Nitrobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

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2,6-Difluorobenzenesulfonic acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester,

Benzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

5 Benzenesulfonic acid 1-benzenesulfonyl-3-(1-methylpiperidine-4-yl)-1H-indol-5-yl ester,

Benzenesulfonic acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester,

10 Benzenesulfonic acid 1-(Benzenesulfonyl) acid 3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl ester,

2,6-Difluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

15 2,6-Difluorobenzenesulfonic acid 1-(2,6-difluorobenzenesulfonyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

2,6-Difluorobenzenesulfonic acid 1-phenethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

20 2,6-Difluorobenzenesulfonic acid 1-(4-fluorobenzyl)-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

2,6-Difluorobenzenesulfonic acid 1-benzyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

4-Fluorobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

25 2,6-Difluorobenzenesulfonic acid 1-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

4-Aminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

30 4-Methylsulfonylaminobenzenesulfonic acid 3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

2,6-Difluorobenzenesulfonic acid 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

2,6-Difluorobenzenesulfonic acid 1,7-dimethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

35 2,6-Difluorobenzenesulfonic acid 7-methyl-1-ethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

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2,6-Difluorobenzenesulfonic acid 7-methyl-1-propyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

2,6-Difluorobenzenesulfonic acid 1-benzyl-7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

5 2,6-Difluorobenzenesulfonic acid 7-methyl-1-phenethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester ,

Benzenesulfonic acid 1,7-dimethyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

10 Benzenesulfonic acid 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

2,6-Dichlorobenzenesulfonic acid 7-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

Benzenesulfonic acid 9-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-yl ester,

15 Benzenesulfonic acid 2-methyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

2,6-Difluorobenzenesulfonic acid 1-isopropyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester,

20 Benzenesulfonic acid 1-cyclohexyl-3-(1-methylpiperidin-4-yl)-1H-indol-5-yl ester, and

Benzenesulfonic acid 7-bromo-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl ester.

25 13. A pharmaceutical composition comprising a compound of anyone of Claims 1 to 6 and a pharmaceutically acceptable diluent.

14. A method of treating disorders associated with the 5-HT₆ antagonism, comprising: administering to a patient in need thereof an effective amount of a compound of anyone of Claims 1 to 6.

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15. A method of treating cognitive disorders, comprising: administering to a patient in need thereof an effective amount of a compound of anyone of Claims 1 to 6.

5 16. A method of treating Alzheimer's disease, comprising: administering to a patient in need thereof an effective amount of a compound of anyone of Claims 1 to 6.

10 17. A method of treating schizophrenia, comprising: administering to a patient in need thereof an effective amount of a compound of anyone of Claims 1 to 6.

18. The use of a compound of Claim 1 as a medicament.

15 19. The use of a compound of anyone of Claims 1 to 6 for the preparation of a medicament for treating disorders associated with the 5-HT₂ antagonism.

20. The use of a compound of anyone of Claims 1 to 6 for the preparation of a medicament for treating cognitive disorders.

20 21. The use of a compound of anyone of Claims 1 to 6 for the preparation of a medicament for treating Alzheimer's disease.

22. The use of a compound of anyone of Claims 1 to 6 for the preparation of a medicament for treating schizophrenia.

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(21) International Application Number: **PCT/US02/00502**

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(25) Filing Language: English

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60/264,996 30 January 2001 (30.01.2001) US

(71) Applicant (for all designated States except US): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FILLA, Sandra, Ann** [US/US]; 14 Belknap Circle, Ashland, MA 01721 (US). **FLAUGH, Michael, Edward** [US/US]; 9224 Kinlock Drive, Indianapolis, IN 46256 (US). **GILLIG, James, Ronald** [US/US]; 3634 Toronto Court, Indianapolis, IN 46268 (US). **HEINZ, Lawrence, Joseph** [US/US]; 212 Fawn Court, Pittsboro, IN 46167 (US). **KRUSHINSKI, Joseph, Herman, Junior** [US/US]; 6915 Windjammer Drive, Brownburg, IN 46112 (US). **LIU, Bin** [CN/US]; 12254 Limestone Drive, Fishers, IN 46038 (US). **PINEIRO-NUNÉZ, Marta, Maria** [ES/US]; 364 Thornburg Parkway, Brownsburg, IN 46112 (US). **SCHAUS, John, Mehnert** [US/US]; 135 Raintree Drive, Zionsville, IN 46077 (US). **WARD, John, Stanley** [US/US]; 812 Corriente Pointe Drive, Redwood City, CA 94065 (US).

(74) Agents: **STEMERICK, David, M. et al.**; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States (national): AE, AG, AL, AM, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), DE (utility model), DK (utility model), DM, DZ, EC, EE (utility model), ES, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

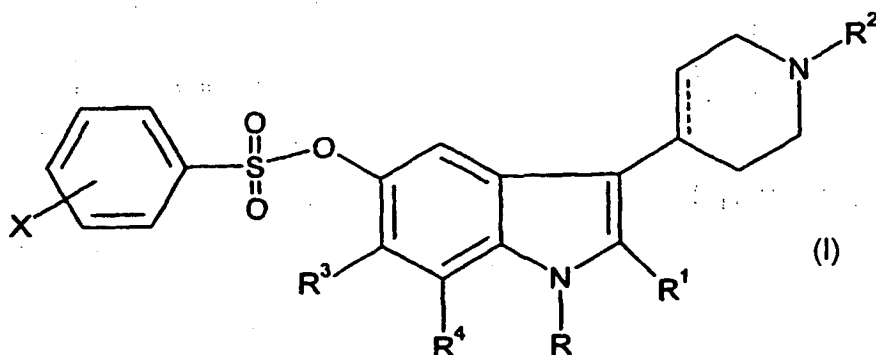
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,

[Continued on next page]

(54) Title: **BENZENESULFONIC ACID INDOL-5-YL ESTERS AS ANTAGONISTS OF THE 5-HT₆ RECEPTOR**



(57) Abstract: The present invention relates to compounds of formula I: which are antagonists of 5-HT₆ receptor.

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BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 C07D401/04 C07D401/14 A61K31/454 A61P25/28
A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 63203 A (ALLELIX BIOPHARMA) 26 October 2000 (2000-10-26) the whole document	1-22
A	WO 93 11106 A (PFIZER) 10 June 1993 (1993-06-10) the whole document	1-22

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

11 June 2003

Date of mailing of the international search report

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Name and mailing address of the ISA

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Authorized officer

Schmid, J-C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/00502

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

In on patent family members

International Application No

PCT/US 02/00502

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0063203	A	26-10-2000	WO 0063203 A1	26-10-2000
			AU 3403599 A	02-11-2000
			CA 2370147 A1	26-10-2000
			EP 1173432 A1	23-01-2002
			JP 2002542241 T	10-12-2002
WO 9311106	A	10-06-1993	AT 190608 T	15-04-2000
			AU 671959 B2	19-09-1996
			AU 2896192 A	28-06-1993
			BR 9206810 A	31-10-1995
			CA 2124206 A1	10-06-1993
			CN 1072679 A ,B	02-06-1993
			CZ 9401280 A3	15-02-1995
			DE 69230803 D1	20-04-2000
			DE 69230803 T2	07-12-2000
			DK 619805 T3	05-06-2000
			EG 21209 A	31-01-2001
			EP 0619805 A1	19-10-1994
			ES 2143992 T3	01-06-2000
			FI 942395 A	24-05-1994
			GR 3033370 T3	29-09-2000
			HU 69705 A2	28-09-1995
			IL 103798 A	13-08-2000
			JP 8239363 A	17-09-1996
			JP 2840448 B2	24-12-1998
			JP 6510793 T	01-12-1994
			KR 184911 B1	01-05-1999
			MX 9206762 A1	01-05-1993
			NO 941918 A	24-05-1994
			NZ 245243 A	21-12-1995
			NZ 272130 A	24-06-1997
			PL 173875 B1	29-05-1998
			PT 101087 A ,B	30-06-1994
			RU 2126399 C1	20-02-1999
			WO 9311106 A1	10-06-1993
			US 5639752 A	17-06-1997
			ZA 9209082 A	24-05-1994

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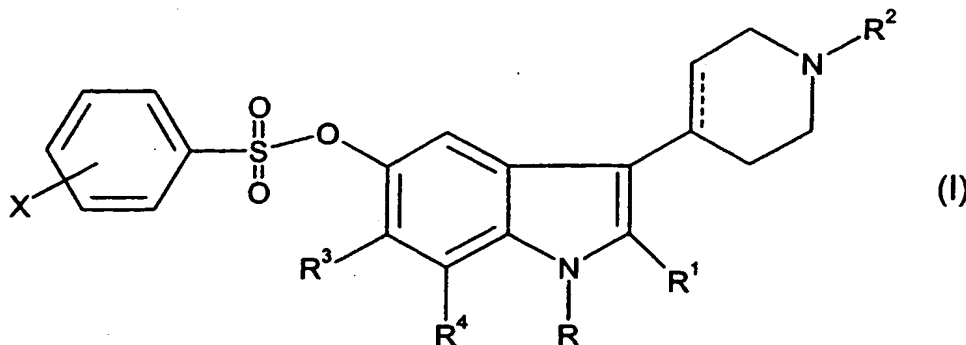
- (51) **International Patent Classification⁷:** C07D 487/04, 401/04, 401/14, A61K 31/454, A61P 25/28, 25/18
- (21) **International Application Number:** PCT/US02/00502
- (22) **International Filing Date:** 17 January 2002 (17.01.2002)
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60/264,996 30 January 2001 (30.01.2001) US
- (71) **Applicant (for all designated States except US):** ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** FILLA, Sandra, Ann [US/US]; 14 Belknap Circle, Ashland, MA 01721 (US). FLAUGH, Michael, Edward [US/US]; 9224 Kinlock Drive, Indianapolis, IN 46256 (US). GILLIG, James, Ronald [US/US]; 3634 Toronto Court, Indianapolis, IN 46268 (US). HEINZ, Lawrence, Joseph [US/US]; 212 Fawn Court, Pittsboro, IN 46167 (US). KRUSHINSKI, Joseph, Herman, Junior [US/US]; 6915 Windjammer Drive, Brownburg, IN 46112 (US). LIU, Bin [CN/US]; 12254 Limestone Drive, Fishers, IN 46038 (US). PINEIRO-NUNEZ, Marta, Maria [BS/US]; 364 Thornburg Parkway, Brownsburg, IN 46112 (US). SCHAUS, John, Mehnert [US/US]; 135 Raintree Drive, Zionsville, IN 46077 (US). WARD, John, Stanley [US/US]; 812 Corriente Pointe Drive, Redwood City, CA 94065 (US).
- (74) **Agents:** STEMERICK, David, M. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).
- (81) **Designated States (national):** AE, AG, AL, AM, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declarations under Rule 4.17:**
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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[Continued on next page]

- (54) Title:** BENZENESULFONIC ACID INDOL-5-YL ESTERS AS ANTAGONISTS OF THE 5-HT₆ RECEPTOR



- (57) Abstract:** The present invention relates to compounds of formula I: which are antagonists of 5-HT₆ receptor.



- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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